

Reference

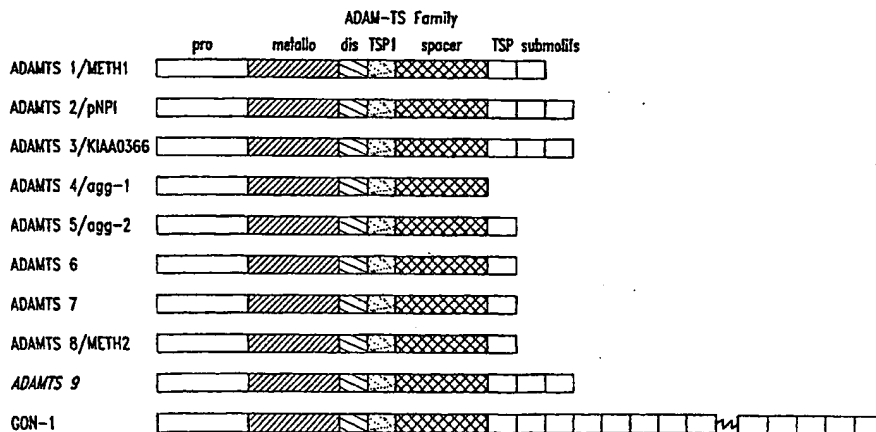
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(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR



(57) Abstract

Novel members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.

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METALLOPROTEINASES AND METHODS OF USE THEREFOR

TECHNICAL FIELD

5 The present invention relates generally to compositions and methods for the treatment of conditions associated with undesirable levels of metalloproteinase activity. The invention is more particularly related to metalloproteinases and agents that modulate the activity of such metalloproteinases which may be used, for example, for the therapy of diseases characterized by neuroinflammation and/or
10 neurodegeneration, as well as autoimmune diseases, cancer and inflammation.

BACKGROUND OF THE INVENTION

 The ADAMs (A Disintegrin and Metalloproteinase Domain) are a family of proteins that have both a metalloproteinase domain and disintegrin domain. The
15 ADAMs are membrane anchored proteins that contain homology to snake venom metalloproteases (SVMPs) and disintegrins. This family of proteins now contains over 20 members that have a wide variety of important proteolytic and cell fusion functions. ADAM 17/TACE and ADAM 10/Kuz function as proteases that cleave membrane bound tumor necrosis factor (TNF) and the extracellular domain of Notch, respectively.
20 Other ADAM family members, such as ADAM 1/fertilin α , are proteolytically processed to remove the metalloprotease domain but retain the disintegrin domain. This protein has been shown to be essential for sperm-egg cell fusion.

 A closely related family called ADAMTS contains a thrombospondin domain in addition to the disintegrin and metalloproteinase domains. ADAMTS-1, for
25 example, is expressed in association with inflammatory processes and in a cachexigenic colon carcinoma cell line (see Kuno et al., *J. Biol. Chem.* 272:556-562, 1997; Kuno et al., *Genomics* 46:466-471, 1997). This protein appears to be secreted from the cell and subsequently associated with the extracellular matrix (ECM).

 While the function of ADAMTS-1 and many of the ADAM proteins is
30 not known, it has been shown that ADAM 17 (TACE) processes TNF from the surface of the cell (see Black et al., *Nature* 385:729-733, 1997). ADAM 10 (Kuzbanian) has

also been shown to cleave TNF from the cell surface (Rosendahl et al., *J. Biol. Chem.* 272:24588-24593, 1997). ADAM 10 may be involved in the cleavage of other cell surface proteins as well. In *Drosophila*, ADAM 10 has been reported to cleave the cell surface proteins Notch (Pan and Rubin, *Cell* 90:271-280, 1997) and Delta (Qi et al.,
5 *Science* 283:91-94, 1999). Based largely on these results it is thought that ADAMs proteases are involved in the cleavage of proteins, including growth factors, cytokines and proteoglycans, from the cell surface.

Metalloproteinase activity has been linked to cancer metastasis. The activity of metalloproteinases can contribute to the development of neurodegeneration
10 and inflammation as well. In order to develop agents capable of selectively modulating the activity of a metalloproteinase that contributes to a human disease, it is important to identify and characterize additional metalloproteinases, such as members of the ADAMTS family, and agents that modulate an activity of such metalloproteinases. The present invention fulfills this need and further provides other related advantages.

15

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides ADAMTS polypeptides, and methods employing such polypeptides. Within certain aspects, isolated polynucleotides that encode an ADAMTS polypeptide are provided. Certain ADAMTS
20 polynucleotides encode an ADAMTS polypeptide that comprises: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no
25 more than 10% of the consecutive residues of the ADAMTS protein. Such polynucleotides may, within certain embodiments, comprise a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.

Within related aspects, the present invention provides recombinant expression vectors comprising an ADAMTS polynucleotide, as well as host cells
30 transformed or transfected with such an expression vector.

The present invention further provides isolated antisense polynucleotides complementary to at least 20 consecutive nucleotides present within an ADAMTS polynucleotide.

Within further aspects, methods are provided for preparing an ADAMTS polypeptide, comprising the steps of: (a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and (b) recovering an ADAMTS polypeptide.

The present invention further provides isolated ADAMTS polypeptides comprising: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein. Such an ADAMTS polypeptide may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. ADAMTS polypeptide may comprise an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are

present at no more than 10% of the consecutive residues of the ADAMTS protein; and
(b) a physiologically acceptable carrier.

Vaccines are also provided, comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that
5 comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) a non-specific immune response enhancer.

10 Within further aspects, the present invention provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind to an ADAMTS polypeptide comprising a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

The present invention further provides methods for screening for agents
15 that modulate ADAMTS protein expression or activity. Within certain such aspects, methods are provided for screening for an agent that modulates ADAMTS protein expression in a cell, comprising: (a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence
20 recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) subsequently evaluating the effect of the candidate modulator on expression of an
25 ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell. Similar screens may be performed using a cell comprising an ADAMTS gene promoter operably linked to a reporter gene, and evaluating the effect of a candidate modulator on expression of the reporter gene.

Within further such aspects, methods are provided for screening for an
30 agent that modulates an ADAMTS protein activity, comprising: (a) contacting a

candidate modulator with an ADAMTS polypeptide, comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein; and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and (b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

ADAMTS polynucleotides, polypeptides and modulating agents may be used for a variety of therapeutic applications. Within certain aspects, methods are provided herein for inhibiting neuroinflammation and/or neurodegeneration in a patient, comprising administering to a patient an agent that decreases an activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27. Certain such agents may inhibit expression of an endogenous ADAMTS gene or may bind to an ADAMTS protein.

Within related aspects, methods are provided for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration, comprising administering to a patient a pharmaceutical composition as described above, and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration. Such conditions include Alzheimer's disease, Parkinson's disease and stroke.

Methods are further provided for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis, comprising administering to a patient a pharmaceutical composition as described above and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration.

Within further aspects, methods are provided for treating a patient afflicted with an invasive tumor, a brain tumor or a brain injury, comprising administering to a patient an agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Methods are further provided for modulating ADAMTS expression and/or activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS activity, wherein the ADAMTS polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and thereby modulating ADAMTS expression and/or activity in the cell.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:1).

Figure 2 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:2).

Figures 3A-3B present a partial sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:3).

Figure 4 presents a partial predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:4).

Figures 5A and 5B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0605 (SEQ ID NO:5).

Figure 6 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0605 (SEQ ID NO:6).

5 Figures 7A and 7B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0366 (SEQ ID NO:7).

Figure 8 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0366 (SEQ ID NO:8).

10 Figures 9A and 9B present the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:9).

Figure 10 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:10).

Figures 11A and 11B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0688 (SEQ ID NO:11).

15 Figure 12 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0688 (SEQ ID NO:12).

Figure 13 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:13).

20 Figure 14 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:14).

Figure 15 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:15).

Figure 16 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:16).

25 Figures 17A-17G present a sequence alignment of human ADAMTS-1 (SEQ ID NO:28), ADAMTS-2 (SEQ ID NO:2), ADAMTS-3 (SEQ ID NO:10), ADAMTS-4 (SEQ ID NO:4), KIAA0688 (SEQ ID NO:12), KIAA0366 (SEQ ID NO:8) and KIAA0605 (SEQ ID NO:6).

30 Figure 18 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:17).

Figure 19 presents the predicted amino acid sequence of the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:18).

Figure 20 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:19).

5 Figure 21 presents the predicted amino acid sequence of the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:20).

Figure 22 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:21).

10 Figure 23 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:22).

Figure 24 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:23).

Figure 25 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:24).

15 Figure 26 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:25).

Figure 27 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:26).

20 Figure 28 is a photograph depicting a coumassie blue-stained gel following electrophoresis of 500 micrograms brevican, previously incubated with and without ADAMTS-4 (TS-4) as indicated.

Figure 29 depicts the amino acid sequence of ADAMTS-9 (SEQ ID NO:27). The predicted signal sequence is underlined. The Zn binding, met turn, TSP 1 motif and TSP-1 like submotifs are shaded. Two potential furin cleavage sites are in parenthesis with the most likely cleavage site shaded. A potential "cysteine switch" amino acid is indicated with a star. The start of each domain is indicated with an arrow.

Figures 30A-30C illustrate the comparison of ADAMTS-9 to other ADAMTS family members. In Figure 30A, the domain structure of human ADAMTS 9 is compared to human ADAMTS 1-8, and also with the *C. elegans* GON-1 protein.

30 The pro-domain, metalloprotease domain, disintegrin-like domain, initial TSP type 1

repeat, spacer region, and TSP1 like submotifs are outlined. Figure 30B shows the consensus sequence for Zn binding in the metalloprotease domain (SEQ ID NO:30), along with the Zn binding site for various ADAM and ADAM-TS proteins (SEQ ID Nos: 42-48, 50) that have active metalloprotease domains for comparison to ADAMTS-9 (SEQ ID NO:49). Conserved residues are shaded. Figure 30C is a dendrogram showing the phylogenetic relationship between the protein sequence of the known ADAM-TS human family members and GON-1 from *C. elegans*.

Figure 31 is a photograph illustrating the tissue distribution pattern of ADAMTS-9 in human fetal and adult cDNA. PCR analysis of several human fetal and adult cDNAs was performed using specific primers to ADAMTS 9. Lanes 2 -16 are human adult tissue cDNAs and lanes 17 - 24 are human fetal cDNAs. Lane 25 is a no cDNA control. The expected product size for these ADAMTS 9 primers is 510 bp. The lower panel contains the same cDNA samples used as a template for PCR with G3PDH primers (expected product size is 1 kb).

Figures 32A and 32B illustrate the chromosomal localization of human ADAMTS-9 to 3p14.3-21.1. Figure 32A is a photograph showing the results of FISH analysis in which a genomic ADAMTS 9 probe hybridized to chromosome 3p. Figure 32B shows two ideograms illustrating the chromosomal position of ADAMTS-9 at 3p14.2-14.3. The International System for Human Cytogenetic Nomenclature 1995 was used.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to polypeptides comprising a member of the ADAMTS family of metalloproteinases, or a variant thereof. Such ADAMTS polypeptides are generally characterized by homology to a known ADAMTS protein, and by the presence of one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain, (c) an ECM domain and/or (d) a thrombospondin type I motif, which may be identified as described herein. The present invention further provides ADAMTS polynucleotides encoding such polypeptides and agents that modulate an activity of such polypeptides. ADAMTS

polypeptides, polynucleotides and/or modulating agents may generally be used for treating conditions associated with undesirable levels of metalloproteinase activity.

ADAMTS POLYNUCLEOTIDES

5 Any polynucleotide that encodes an ADAMTS polypeptide as described herein is encompassed by the present invention. Such polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a
10 polynucleotide may, but need not, be linked to other molecules and/or support materials.

ADAMTS polynucleotides may comprise a native ADAMTS sequence (*i.e.*, an ADAMTS gene that can be found in an organism that is not genetically modified), or may comprise a variant of such a sequence. Native ADAMTS sequences
15 encompassed by the present invention include DNA and RNA molecules that comprise a sequence recited in any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 or 25 as well as homologues thereof from other species and other native ADAMTS sequences that may be identified based on homology to a sequence recited herein. Polynucleotide variants may contain one or more substitutions, additions, deletions
20 and/or insertions such that an ADAMTS activity of the encoded polypeptide is not diminished, relative to a native ADAMTS protein. The effect on an activity of the encoded polypeptide may generally be assessed as described herein. Preferred variants contain nucleotide substitutions, deletions, insertions and/or additions at no more than 30%, preferably at no more than 20% and more preferably at no more than 10%, of the
25 nucleotide positions. Certain variants are substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding an ADAMTS polypeptide (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5%
30 SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed

by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention.

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense oligonucleotides may be synthesized directly, or cDNA constructs that can be transcribed into antisense RNA may be introduced into cells or tissues to facilitate the production of antisense RNA. Antisense oligonucleotides are preferably at least 20 nucleotides in length, preferably at least 30 nucleotides in length. A portion of a coding sequence or a complementary sequence may also be designed as a probe or primer to detect gene expression. Probes may be labeled by a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers are preferably 22-30 nucleotides in length.

ADAMTS polynucleotides may be prepared using any of a variety of techniques. For example, an ADAMTS polynucleotide may be amplified from cDNA prepared from cells that express an ADAMTS protein (*e.g.*, microglia, macrophages, myeloid cells, lymphocytes, astrocytes oligodendrocytes, glial cells, neurons, epithelial cells and/or endothelial cells). Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed

based on the sequences provided herein, and may be purchased or synthesized. An amplified portion may then be used to isolate a full length gene from a human genomic DNA library or from a suitable cDNA library, using well known techniques. Alternatively, a full length gene can be constructed from multiple PCR fragments.

5 ADAMTS polynucleotides may also be prepared by synthesizing oligonucleotide components (which may be derived from sequences provided herein), and ligating components together to generate the complete polynucleotide. One other approach is to screen a library with a synthesized oligonucleotide that hybridizes to an ADAMTS gene. Libraries may generally be prepared and screened using methods well known to

10 those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. It has been found, within the context of the present invention, that ADAMTS genes are expressed in glia. Accordingly, one suitable library is a microglia (e.g., rat) cDNA library. Other libraries that may be employed will be apparent to those

15 of ordinary skill in the art.

As noted above, polynucleotides comprising portions and other variants of native ADAMTS sequences are within the scope of the present invention. Such polynucleotides may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis.

20 Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding an ADAMTS polypeptide, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Variants may also be generated by mutagenesis or enzymatic digestion of native sequences. Certain polynucleotides may be used to prepare an encoded polypeptide, as

25 described herein. In addition, or alternatively, a polynucleotide may be administered to a patient such that the encoded polypeptide is generated *in vivo*.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather

30 than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional

bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for polynucleotides for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

ADAMTS POLYPEPTIDES

As used herein, the term "ADAMTS polypeptide" encompasses amino acid chains of any length. For example, an ADAMTS polypeptide may comprise a full length endogenous (*i.e.*, native) ADAMTS protein. Such an ADAMTS polypeptide may consist entirely of a native ADAMTS sequence, or may contain additional heterologous sequences. Native ADAMTS proteins may generally be identified based on sequence homology to known ADAMTS protein sequences, such as the representative sequences provided herein, particularly within disintegrin, metalloproteinase and/or thrombospondin motifs. In general, a protein is considered to be an ADAMTS protein if at least 20 consecutive amino acid residues, preferably 40 consecutive amino acids, are identical to a known ADAMTS protein. Alternatively, or in addition, an ADAMTS protein may comprise at least 100 consecutive amino acids that are substantially similar to residues within a known ADAMTS metalloproteinase. "Substantial similarity," as used herein, refers to a sequence that is at least 50% identical, and preferably at least 80% identical.

An ADAMTS protein further comprises one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain and/or (c) a thrombospondin type I motif; and displays at least one, activity characteristic of such a domain or motif. In general a disintegrin domain serves as an integrin binding loop and has a sequence similar to AVN(E/D)CD (SEQ ID NO:29). Disintegrin domains can also contain the sequence RGD. The metalloproteinase domain is based on the presence of an extended catalytic site consensus sequence (HEXXHXXGXXHD; SEQ ID NO:30). It is thought that the three histidines bind the zinc, the glutamic acid is the catalytic base and the glycine allows an important structural turn (Stocker et al., *Protein Science* 4:823-840, 1995). The thrombospondin domain contains the sequence motif CSRTCG (SEQ ID NO:31).

Another domain that may be present within an ADAMTS protein is a domain that binds to the extracellular matrix. This has been referred to as the ECM domain and has the semiconserved sequence FREEQC (SEQ ID NO:32).

In certain embodiments, amino acid residues within a "substantially similar" region may contain primarily or entirely conservative substitutions. A conservative substitution is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity on polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

An ADAMTS polypeptide may comprise a portion of a native ADAMTS protein. Such a portion is preferably at least 20 consecutive amino acid residues in length, more preferably at least 50 consecutive amino acid residues in length. Within certain embodiments, the portion retains an ADAMTS activity that is not substantially diminished relative to the full length ADAMTS protein. Certain ADAMTS polypeptides comprise a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Alternatively, an ADAMTS polypeptide may comprise a variant of an ADAMTS protein or portion thereof. A "variant" is a polypeptide that differs in sequence from a native ADAMTS protein only in substitutions, deletions, insertions and/or additions. Within certain embodiments, substitutions are made (if at all) at no more than 30%, preferably at no more than 20% and more preferably at no more than 10% of residues within a portion of a native ADAMTS protein, as described above. Substitutions are preferably conservative, as described above. Substitutions, deletions and/or amino acid additions may be made at any location(s) in the polypeptide,

provided that the modification does not diminish at least one ADAMTS activity. Thus, a variant may comprise only a portion of a native ADAMTS sequence. In addition, or alternatively, variants may contain additional amino acid sequences (such as, for example, linkers, tags and/or ligands), preferably at the amino and/or carboxy termini.

5 Such sequences may be used, for example, to facilitate purification, detection or cellular uptake of the polypeptide.

Certain variants retain an activity of the native ADAMTS protein. In other words, the variant has a metalloproteinase activity; (2) functions as an integrin ligand (*i.e.*, binds to an integrin), as determined by any standard binding assay; and/or

10 (3) retains a functional thrombospondin motif. Such a variant may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. In other words, the ADAMTS activity of the variant may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein.

15 Also encompassed by the present invention are splice variants of an ADAMTS protein. Such variants may have one or more of the domains described herein deleted, or one or more such domains may be replaced by a domain providing a different function. Such splice variants may be identified using amplification or hybridization techniques described herein.

20 Dominant negative forms of ADAMTS proteins are also provided. Such forms include fragments and variants of an ADAMTS protein that, when introduced to a cell expressing a native ADAMTS protein, inhibit an activity of the native protein. Inhibition of ADAMTS protein activity may be assessed as described herein.

In general, ADAMTS polypeptides may be prepared using any of a

25 variety of techniques that are well known in the art. For example, polypeptides of the present invention may be prepared by expression of recombinant DNA encoding the polypeptide in cultured host cells. Preferably, the host cells are bacteria, yeast, insect or mammalian cells. The recombinant DNA may be cloned into any expression vector suitable for use within the host cell and transfected into the host cell using techniques

30 well known to those of ordinary skill in the art. An expression vector generally contains

a promoter sequence that is active in the host cell. A tissue specific promoter may also be used, as long as it is activated in the target cell. Preferred promoters express the polypeptide at high levels.

Optionally, the construct may contain an enhancer, a transcription
5 terminator, a poly(A) signal sequence, a bacterial or mammalian origin of replication and/or a selectable marker, all of which are well known in the art. Enhancer sequences may be included as part of the promoter region used or separately. Transcription terminators are sequences that stop RNA polymerase-mediated transcription. The poly(A) signal may be contained within the termination sequence or incorporated
10 separately. A selectable marker includes any gene that confers a phenotype on the host cell that allows transformed cells to be identified. Such markers may confer a growth advantage under specified conditions. Suitable selectable markers for bacteria are well known and include resistance genes for ampicillin, kanamycin and tetracycline. Suitable selectable markers for mammalian cells include hygromycin, neomycin, genes
15 that complement a deficiency in the host (*e.g.* thymidine kinase and TK⁻ cells) and others well known in the art.

ADAMTS polypeptides may be expressed in transfected cells by culturing the cell under conditions promoting expression of the transfected polynucleotide. Appropriate conditions will depend on the specific host cell and
20 expression vector employed, and will be readily apparent to those of ordinary skill in the art. For commercially available expression vectors, the polypeptide may generally be expressed according to the manufacturer's instructions. Expressed polypeptides of this invention are generally isolated in substantially pure form. Preferably, the polypeptides are isolated to a purity of at least 80% by weight, more preferably to a
25 purity of at least 95% by weight, and most preferably to a purity of at least 99% by weight. In general, such purification may be achieved using, for example, the standard techniques of ammonium sulfate fractionation, SDS-PAGE electrophoresis, and/or affinity chromatography.

Such techniques may be used to prepare native polypeptides or variants
30 thereof. For example, variants of a native polypeptide may generally be prepared from

polynucleotide sequences modified via standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis, and sections of the DNA sequence may be removed to permit preparation of truncated polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptides and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

EVALUATION OF ADAMTS ACTIVITY

As noted above, native ADAMTS proteins and certain variants thereof possess ADAMTS activity. In other words, such polypeptides (1) possess metalloproteinase activity; (2) are capable of interacting with integrin and/or (3) retain a functional thrombospondin motif. Metalloproteinase activity may generally be evaluated by combining an ADAMTS polypeptide with a suitable substrate, and detecting proteinase activity using any standard technique (*e.g.*, Western blot analysis). In general, a variant of an ADAMTS protein that contains a metalloproteinase domain is said to retain metalloproteinase activity if it displays metalloproteinase activity that is not substantially diminished relative to the metalloproteinase activity of the native

ADAMTS protein. In other words, such activity may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

The ability of an ADAMTS protein variant to interact with integrin may be assessed using standard binding assays to detect interaction with a purified recombinant integrin or a cell expressing one or more integrins, either naturally or as a result of transfection with genes encoding an integrin (*see* Almeida et al., *Cell* 81:1095-1104, 1995; Chen et al., *J. Cell Biol.* 144:549-561, 1999). Antibodies against various integrins can also be used to interfere with disintegrin-integrin binding and used to further demonstrate specificity of the interaction. In general, a variant of an ADAMTS protein is said to retain the ability to interact with an integrin if such interaction is not substantially diminished relative to the interaction between a native ADAMTS protein and the integrin. In other words, the level of such an interaction may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

Thrombospondins have been shown to function in cell adhesion, cell migration, cell proliferation and angiogenesis. A functional thrombospondin motif may be confirmed based on any assay designed to assess such a function. For examples, an ADAMTS protein may inhibit endothelial cell migration, or may inhibit angiogenesis (*e.g.*, in a rat cornea model; *see* Nishimori et al., *Oncogene* 15:2145-2150, 1997). Alternatively, a functional thrombospondin motif may be detected using an assay to measure binding to CD36 (*see* Dawson et al., *J. Cell. Biol.* 138:707-717, 1997). Within any such assay, a variant of an ADAMTS protein is said to have a functional thrombospondin motif if the detected thrombospondin function is not substantially diminished relative to that of the native ADAMTS protein. In other words, the function may be enhanced, unchanged or diminished by less than 10%, relative to that of the native ADAMTS protein.

ADAMTS POLYPEPTIDE MODULATING AGENTS

The present invention further provides agents capable of modulating ADAMTS activity. Such agents may function by modulating ADAMTS transcription

or translation, by stabilizing or destabilizing an ADAMTS protein, or by directly inhibiting or enhancing an activity of an ADAMTS protein. Alternatively, an agent may interact with a substrate for the metalloproteinase or with an integrin involved in and interaction with the disintegrin domain of an ADAMTS protein. Preferably, a
5 modulating agent has a minimum of side effects and is non-toxic. For some applications, agents that can penetrate cells or that are targeted to interstitial spaces are preferred.

Modulating agents include substances that selectively bind to an ADAMTS protein. Such substances include antibodies and antigen-binding fragments
10 thereof (*e.g.*, F(ab)₂, Fab, Fv, V_H or V_K fragments), as well as single chain antibodies, multimeric monospecific antibodies or fragments thereof and bi- or multi-specific antibodies and fragments thereof. Antibodies that bind to an ADAMTS protein may be polyclonal or monoclonal, and are specific for an ADAMTS polypeptide (*i.e.*, bind to such a peptide detectable within any appropriate binding assay, and do not bind to an
15 unrelated protein in a similar assay under the same conditions). Preferred antibodies are those antibodies that function as modulating agents to inhibit or block an ADAMTS activity *in vivo*. Antibodies may also be employed within assays for detecting the level of ADAMTS protein within a sample.

Antibodies may be prepared by any of a variety of techniques known to
20 those of ordinary skill in the art (*see, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988). In one such technique, an immunogen comprising the polypeptide is initially injected into a suitable animal (*e.g.*, mice, rats, rabbits, sheep and goats), preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.
25 Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements
30 thereto. Briefly, these methods involve the preparation of immortal cell lines capable of

producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction.

Once a cell line, such as a hybridoma, expressing an antibody that specifically binds to an ADAMTS protein has been obtained, other chimeric antibodies and fragments thereof as described herein may be prepared. Using well known techniques, a cDNA molecule encoding the antibody may be identified.

Other modulating agents include peptides, and nonpeptide mimetics thereof, that specifically interact with one or more regions of an ADAMTS polypeptide. Such agents may generally be identified using any well known binding assay, such as a representative assay provided herein. For example, such modulating agents may be isolated using well known techniques to screen substances from a variety of sources, such as plants, fungi or libraries of chemicals, small molecules or random peptides.

Other modulating agents may function by inhibiting or enhancing transcription or translation of an ADAMTS gene. For example, modulating agents may include antisense polynucleotides (DNA or RNA), which inhibit the transcription of a native ADAMTS protein. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. Antisense technology can generally be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., *In Huber and Carr, Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense polynucleotides are generally at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length.

Other agents may modulate transcription by interacting with an ADAMTS promoter. Such agents may be identified using standard assays, following isolation of an endogenous ADAMTS gene promoter region. One method for identifying a promoter region uses a PCR-based method to clone unknown genomic DNA sequences adjacent to a known cDNA sequence. This approach may generate a 5' flanking region, which may be subcloned and sequenced using standard methods. Primer extension and/or RNase protection analyses may be used to verify the transcriptional start site deduced from the cDNA.

To define the boundary of the promoter region, putative promoter inserts of varying sizes may be subcloned into a heterologous expression system containing a suitable reporter gene without a promoter or enhancer may be employed. Internal deletion constructs may be generated using unique internal restriction sites or by partial digestion of non-unique restriction sites. Constructs may then be transfected into cells that display high levels of ADAMTS protein expression. In general, the construct with

the minimum 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter.

To evaluate the effect of a candidate agent on ADAMTS gene transcription, a promoter or regulatory element thereof may be operatively linked to a reporter gene. Such a construct may be transfected into a suitable host cell, which may be used to screen, for example, a combinatorial small molecule library. Briefly, cells are incubated with the library (*e.g.*, overnight). Cells are then lysed and the supernatant is analyzed for reporter gene activity according to standard protocols. Compounds that result in a decrease in reporter gene activity are inhibitors of ADAMTS gene transcription.

For modulating agents that act directly on an ADAMTS protein, an initial screen to assess the ability of candidate agents to bind to such a protein may be employed, although such binding is not essential for a modulating agent. For identifying agents that bind to an ADAMTS polypeptide, any of a variety of binding assays may be employed, such as standard affinity techniques and yeast two-hybrid screens. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. An antibody or other modulating agent is said to "specifically bind" to an ADAMTS polypeptide if it reacts at a detectable level with such a polypeptide and does not react detectably with unrelated polypeptides. Such antibody binding properties may be assessed using, for example, an ELISA.

Screens for modulating agents that increase the rate of ADAMTS protein synthesis or stabilize ADAMTS protein may be readily performed using well known techniques that detect the level of ADAMTS protein or mRNA. Suitable assays include RNA protection assays, *in situ* hybridization, ELISAs, Northern blots and Western blots. Such assays may generally be performed using standard methods (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). For example, to detect mRNA encoding ADAMTS protein, a nucleic acid probe complementary to all or a portion of an ADAMTS gene sequence may be employed in a Northern blot analysis of mRNA prepared from suitable cells (*e.g.*, brain, lung, heart, spleen, spinal cord, testis, astrocytes or microglia).

To detect ADAMTS protein, a reagent that binds to the protein (typically an antibody) may be employed within an ELISA or Western assay. Following binding, a reporter group suitable for direct or indirect detection of the reagent is employed (*i.e.*, the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.*, horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those of ordinary skill in the art.

To use such assays for identifying a modulating agent, the level of ADAMTS protein or mRNA is evaluated in cells (*e.g.*, astrocytes or microglia) treated with one or more candidate modulating agents. An increase or decrease in ADAMTS levels may be measured by evaluating ADAMTS mRNA and/or protein in the presence and absence of candidate modulating agent. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. A candidate that results in a statistically significant change in the level of ADAMTS mRNA and/or protein is a modulating agent.

Modulating agents that decrease ADAMTS levels generally inhibit ADAMTS activity. To further evaluate the effect on ADAMTS activity, an assay may be performed as described above in the presence and absence of modulating agent. Agents that bind to a substrate of an ADAMTS protein domain may also be identified using such assays. Modulating agents may generally be administered by addition to a cell culture or by the methods described below for *in vivo* administration.

ADAMTS POLYPEPTIDE AND MODULATING AGENT MODIFICATION AND FORMULATIONS

An ADAMTS polypeptide or modulating agent as described herein may, but need not, be linked to one or more additional molecules. In particular, as discussed below, it may be beneficial for certain applications to link multiple polypeptides and/or modulating agents (which may, but need not, be identical) to a support material, such as

a polymeric matrix or a bead or other particle, which may be prepared from a variety of materials including glass, plastic or ceramics. For certain applications, biodegradable support materials are preferred.

Suitable methods for linking an ADAMTS polypeptide or modulating agent to a support material will depend upon the composition of the support and the intended use, and will be readily apparent to those of ordinary skill in the art. Attachment may generally be achieved through noncovalent association, such as adsorption or affinity or, preferably, via covalent attachment (which may be a direct linkage or may be a linkage by way of a cross-linking agent).

It may be beneficial for certain applications to link an ADAMTS polypeptide or modulating agent to a targeting agent to facilitate targeting to one or more specific tissues. As used herein, a "targeting agent," may be any substance (such as a compound or cell) that, when linked to a polypeptide or modulating agent enhances the transport of the polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Targeting agents include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. Known targeting agents include serum hormones, antibodies against cell surface antigens, lectins, adhesion molecules, tumor cell surface binding ligands, steroids, cholesterol, lymphokines, fibrinolytic enzymes and those drugs and proteins that bind to a desired target site. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Within other embodiments, it may also be possible to target a polynucleotide encoding a polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Such targeting may be achieved using well known techniques, including retroviral and adenoviral infection. To treat a patient afflicted with certain conditions (e.g., neurodegenerative conditions), it may be beneficial to deliver an ADAMTS polypeptide, polynucleotide or modulating agent to the intracellular space. Such targeting may be achieved using well known

techniques, such as through the use of polyethylene glycol or liposomes, as described in Turens, *Xenobiotica* 21:1033-1040, 1991.

For certain embodiments, it may be beneficial to also, or alternatively, link a drug to a polypeptide or modulating agent. As used herein, the term "drug" refers to any bioactive agent intended for administration to a mammal to prevent or treat a disease or other undesirable condition.

Within certain aspects of the present invention, one or more polypeptides, polynucleotides or modulating agents as described herein may be present within a pharmaceutical composition or vaccine. A pharmaceutical composition further comprises one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants and liposomes.

To prepare a pharmaceutical composition, an effective amount of one or more polypeptides, polynucleotides and/or modulating agents is mixed with a suitable pharmaceutical carrier. Solutions or suspensions used for parenteral, intradermal, subcutaneous or topical application can include, for example, a sterile diluent (such as water), saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol or other synthetic solvent; antimicrobial agents (such as benzyl alcohol and methyl parabens); antioxidants (such as ascorbic acid and sodium bisulfite) and chelating agents (such as ethylenediaminetetraacetic acid (EDTA)); buffers (such as acetates, citrates and phosphates). If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropylene glycol and mixtures thereof. In addition, other pharmaceutically active ingredients and/or suitable excipients such as salts, buffers and stabilizers may, but need not, be present within the composition.

A pharmaceutical composition is generally formulated and administered to exert a therapeutically useful effect while minimizing undesirable side effects. The

number and degree of acceptable side effects depend upon the condition for which the composition is administered. For example, certain toxic and undesirable side effects that are tolerated when treating life-threatening illnesses, such as tumors, would not be tolerated when treating disorders of lesser consequence. The concentration of active
5 component in the composition will depend on absorption, inactivation and excretion rates thereof, the dosage schedule and the amount administered, as well as other factors that may be readily determined by those of skill in the art.

A polypeptide, polynucleotide or modulating agent may be prepared with carriers that protect it against rapid elimination from the body, such as time release
10 formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others known to those of ordinary skill in the art. Such formulations may generally be prepared using well known technology and
15 administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polynucleotide, polypeptide or modulating agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Preferably the formulation provides a relatively constant level of modulating agent release. The
20 amount of active component contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented).
25 Administration may be effected by incubation of cells *ex vivo* or *in vivo*, such as by topical treatment, delivery by specific carrier or by vascular supply. Appropriate dosages and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease and the method of administration. In general, an appropriate dosage and treatment
30 regimen provides the polypeptide, polynucleotide and/or modulating agent(s) in an

amount sufficient to provide therapeutic and/or prophylactic benefit (*i.e.*, an amount that ameliorates the symptoms or treats or delays or prevents progression of the condition). The precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by testing the compositions in model systems known in the art and extrapolating therefrom. Dosages may also vary with the severity of the condition to be alleviated. The composition may be administered one time, or may be divided into a number of smaller doses to be administered at intervals of time. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art, and for any particular subject, specific dosage regimens may be adjusted over time according to the individual need.

For pharmaceutical compositions comprising polynucleotides, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid, bacterial and viral expression systems, and colloidal dispersion systems such as liposomes. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal, as described above). The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993.

Various viral vectors that can be used to introduce a nucleic acid sequence into the targeted patient's cells include, but are not limited to, vaccinia or other pox virus, herpes virus, retrovirus, or adenovirus. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus including, but not limited to, Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a gene that

encodes the ligand for a receptor on a specific target cell (to render the vector target specific).

Viral vectors are typically non-pathogenic (defective), replication competent viruses, which require assistance in order to produce infectious vector particles. This assistance can be provided, for example, by using helper cell lines that contain plasmids that encode all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR, but that are missing a nucleotide sequence which enables the packaging mechanism to recognize an RNA transcript for encapsulation. Such helper cell lines include (but are not limited to) Ψ2, PA317 and PA12. A retroviral vector introduced into such cells can be packaged and vector virion produced. The vector virions produced by this method can then be used to infect a tissue cell line, such as NIH 3T3 cells, to produce large quantities of chimeric retroviral virions.

Another targeted delivery system for polynucleotides is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). RNA, DNA and intact virions can be encapsulated within the aqueous interior and delivered to cells in a biologically active form. The preparation and use of liposomes is well known to those of ordinary skill in the art.

THERAPEUTIC APPLICATIONS

As noted above, ADAMTS polynucleotides, polypeptides and modulating agents may generally be used for the therapy of diseases characterized by neuroinflammation or neurodegeneration. In general, ADAMTS metalloproteinases are believed to function in cleaving proteins from cell surfaces (which may be surfaces of cells that synthesize the metalloproteinase or other cells). Pharmaceutical compositions as provided herein may be administered to a patient, alone or in combination with other therapies, to treat or prevent neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease or stroke. Pharmaceutical compositions provided herein may also be beneficial for therapy of conditions related to cell proliferation, cell migration, inflammation or angiogenesis. Such conditions include cancer, arthritis and autoimmune diseases.

5 Modulation of an ADAMTS function, either *in vitro* or *in vivo*, may generally be achieved by administering a modulating agent that inhibits ADAMTS transcription, translation or activity. In some instances, however, the ADAMTS activity may be lower than is desired. In such cases, polynucleotides, polypeptides and/or modulating agents that enhance ADAMTS activity may be administered. The activity
10 of an endogenous ADAMTS protein within a cell may be increased by, for example, inducing expression of the ADAMTS gene and/or administering a modulating agent that enhances ADAMTS activity. Each of these methods may be performed using mammalian cells in culture or within a mammal, such as a human.

Certain ADAMTS polypeptides may be used to cleave the proteoglycan
15 brevican. Brevican is a brain specific proteoglycan. The secreted form of brevican is upregulated in response to CNS injury and has been implicated in reactive gliosis, and a cleaved form may be important for tumor invasion (*see* Zhang et al., *J. Neuroscience* 18:2370-76, 1998). Thus, brevican cleavage appears to be important in brain injury and gliomas. Modulating agents that inhibit the ability of such ADAMTS polypeptides to
20 cleave brevican may be used to treat brain injuries, brain tumors and other invasive tumors.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by
25 injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. A suitable dose is an amount of a compound that, when administered as described above, is capable of causing modulation of an ADAMTS activity that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared
30 to non-vaccinated patients. In general, an appropriate dosage and treatment regimen

provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. In general, suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

DIAGNOSTIC APPLICATIONS

In a related aspect of the present invention, kits for detecting ADAMTS proteins are provided. Such kits may be designed for detecting the level of ADAMTS protein or nucleic acid encoding an ADAMTS protein within a sample. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of ADAMTS protein or nucleic acid typically contains a reagent that binds to the ADAMTS protein, DNA or RNA. To detect nucleic acid, the reagent may be a nucleic acid probe or a PCR primer. To detect protein, the reagent is typically an antibody. A kit may also contain a reporter group suitable for direct or indirect detection of the reagent as described above.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1Preparation of Novel ADAMTS Family Members

This Example illustrates the cloning of cDNA molecules encoding members of the ADAMTS family of metalloproteinases based on induction of expression in rat glial cells by aggregated beta amyloid.

Subtractive hybridization was performed as described (Kelner and Maki, *Methods in Molecular Medicine*, vol 22: *Neurodegeneration Methods and Protocols*, Eds J. Harry and H.A. Tilson, Human Press Inc., Totowa, NJ). Briefly, rat glial cells were cultured and treated with aggregated beta amyloid. After 24 hours, RNA was prepared from these cells and from control cells that were not treated with beta amyloid. Genes expressed in the activated cells but not the control cells were sequenced. This screen identified rat ADAMTS-3 (cDNA and encoded protein sequences shown in Figure 26 (SEQ ID NO:25) and Figure 27 (SEQ ID NO:26), respectively). The rat cDNA was used to screen a human cDNA library and resulted in the isolation of human ADAMTS-3. ADAMTS-3 is 2,866 nucleotides in length (Figures 9A and 9B; SEQ ID NO:9) and codes for a putative protein that is 955 amino acids in length (Figure 10; SEQ ID NO:10). ADAMTS-3 contains a metalloproteinase domain, a disintegrin domain, thrombospondin motifs and an ECM domain.

Example 2Preparation of Novel ADAMTS Family Members using Degenerate PCR

This Example illustrates the use of degenerate PCR to clone partial cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

PCR was performed using rat microglia cDNA and degenerate oligonucleotides derived from an analysis of the sequence from ADAMTS-1 and ADAMTS-3. Degenerate primers were designed based on common sequences between

these two genes. The original degenerate primers were designed based on a small region of these two genes that was cloned. One primer had the sequence 5'-TTYMGNGARGARCARTGY-3' (SEQ ID NO:33), while the other primer had the sequence 5'-RCANAYNCCRCAYTTTRTC-3' (SEQ ID NO:34). The PCR conditions were annealing at 47°C for 1 minute, 72°C extension for 2 minutes and 94°C denaturation for 30 seconds.

Following PCR samples were fractionated by gel electrophoresis and fragments of the expected size were cloned into the vector pCRScript and sequenced. One amplified cDNA molecule was designated rat ADAMTS-2 (Figure 24; SEQ ID NO:23), and the encoded protein has the predicted sequence shown in Figure 25 (SEQ ID NO:24). This cDNA was used to screen a human cDNA library, from which human ADAMTS-2 was identified. Human ADAMTS-2 has the sequence shown in Figure 1 (SEQ ID NO:1), and appears to encode the protein recited in Figure 2 (SEQ ID NO:2).

Rat ADAMTS-4 was isolated using the PCR approach and is a polynucleotide having the sequence shown in Figures 3A and 3B (SEQ ID NO:3), which appears to encode the protein recited in Figure 4 (SEQ ID NO:4). For rat ADAMTS-4 the metalloproteinase domain begins at amino acid 260(R), the disintegrin domain begins at residue 487(Q), a thrombospondin motif begins at residue 570(W) and an ECM domain begins at residue 621(C). The rat ADAMTS-4 sequence was used to screen a human cDNA library and human ADAMTS-4 was isolated. Human ADAMTS-4 is 1455 nucleotides in length (Figure 15; SEQ ID NO:15) and codes for a putative protein that is 485 amino acids in length (Figure 16; SEQ ID NO:16). The disintegrin domain in human ADAMTS-4 begins at amino acid 39(E), the start of the first thrombospondin repeat is at amino acid 124(W) and the start of another thrombospondin repeat is at amino acid 479(C). Bovine ADAMTS-4 cDNA has the sequence shown in Figure 18 (SEQ ID NO:17), encoding the predicted amino acid sequence shown in Figure 19 (SEQ ID NO:18).

Rat ADAMTS-5 is a cDNA molecule with the sequence shown in Figure 13 (SEQ ID NO:13), encoding the amino acid sequence shown in Figure 14 (SEQ ID

NO:14). The human ADAMTS cDNA and protein sequences are shown in Figure 22 (SEQ ID NO:21) and Figure 23 (SEQ ID NO:22), respectively.

ADAMTS-4 was further shown to cleave the brain-specific proteoglycan brevican. Five hundred micrograms of purified brevican was cleaved with 500
5 micrograms of human ADAMTS-4 and incubated overnight at 37°C. The cleavage reaction was vacuum dried and resuspended in SDS sample loading dye for running on a 4-20% SDS polyacrylamide gel. Equal amounts of cleaved and uncleaved brevican were added to the gel. After electrophoresis the gel was stained with Coumassie Blue to visualize the protein bands. The results, presented in Figure 30, show that brevican is
10 cleaved upon incubation with ADAMTS-4.

Example 3

Identification of ADAMTS Family Members using Database Searches

15 This Example illustrates the use of database searches to identify cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

To identify additional members of the ADAMTS family, the GenBank database was searched for sequences similar to ADAMTS-1 and ADAMTS-3. This search retrieved KIAA0605 (Figures 5A and 5B; SEQ ID NO:5), which appears to
20 encode a protein of 951 amino acids (Figure 6; SEQ ID NO:6). The coding sequence contains thrombospondin motifs, but no metalloproteinase or disintegrin domains have been identified. A thrombospondin motif begins with amino acid 50(W). Six additional thrombospondin motifs were found beginning with amino acid 568(K). The domain that binds to the extracellular matrix begins with amino acid 105(C).

25 Also retrieved was KIAA0366 (Figures 7A and 7B; SEQ ID NO:7), which appears to encode a protein of 951 amino acids (Figure 8; SEQ ID NO:8), including metalloproteinase and disintegrin domains, as well as thrombospondin motifs. For KIAA0366, the metalloproteinase domain begins with amino acid 241(T), the disintegrin domain begins with amino acid 460(D), a thrombospondin domain is present
30 beginning at position 544(W) and another thrombospondin repeat occurs at position

842(W). The ECM domain begins at amino acid 597(C) and contains the semiconserved sequence FREEQC (SEQ ID NO:32). KIAA0366 does not appear to have a transmembrane domain, and therefore is likely to encode a secreted protein.

An additional sequence identified in this search was KIAA0688 (Figures 11A and 11B; SEQ ID NO:11), which appears to encode the protein shown in Figure 12 and SEQ ID NO:12. This gene codes for a protein with a metalloproteinase domain beginning at amino acid 245(R), a disintegrin domain beginning at amino acid 465(E), a thrombospondin motif at position 550(W), an ECM domain at position 601(C) and two additional thrombospondin motifs at position 905(W). A bovine KIAA0688 cDNA sequence is shown in Figure 20 (SEQ ID NO:19), and the predicted amino acid sequence of the encoded protein is shown in Figure 21 (SEQ ID NO:20).

Figures 17A-17G present an alignment of the ADAMTS protein sequences described herein, along with ADAMTS-1.

Example 4

Identification and Characterization of ADAMTS-9

This Example illustrates the cloning and characterization of the ADAMTS/metalloprotein family member designated herein as ADAMTS-9.

A small fragment of the rat ADAMTS-9 gene was initially cloned from a beta amyloid-treated (35 µg/ml aggregated Aβ 1-42) rat astrocyte cDNA library. DNA sequence analysis was performed using a PCR procedure employing fluorescent dideoxynucleotides and a model ABI-377 automated sequencer (PE Biosystem). BLAST sequence analysis revealed low homology at the protein level to the spacer region of the murine ADAMTS-1 gene.

This clone was labeled with [α -³²P]dCTP using the Prime It II kit (Stratagene) and used to screen a human spinal cord phage library (Clontech) according to the manufacturer's instructions. Positive plaques were purified and lambda DNA prepared (Qiagen). Several overlapping clones were sequenced that had homology to the original rat clone. In order to determine the 5' and 3' ends of the gene RACE (rapid

amplification of cDNA ends) analysis was performed using Marathon Ready placenta and fetal cDNA libraries (Clontech) with SMART primers (Clontech). Overlapping sequence was used to confirm the full length clone. The full length protein sequence of human ADAMTS-9 is shown in Figure 29. The 5' end of the clone contains a methionine codon within a good Kozak consensus for translation initiation. A signal peptide sequence is located just downstream of this methionine in the translated ORF, and the size of the pro-domain is similar to that of other ADAM-TS family members. Therefore, this appears to be the starting methionine of ADAMTS-9.

The overall protein sequence of ADAMTS-9 is similar to that of the other ADAM-TS proteins. All of these family members have a pro-domain, metalloprotease domain, disintegrin-like domain, thrombospondin domain, spacer region, and a variable number of a thrombospondin-like submotifs at the carboxyl-terminal end of the protein (Figure 32A). Like other ADAM-TS family members, ADAMTS 9 contains an amino-terminal signal peptide sequence and lacks a transmembrane domain.

Among the 23 ADAM family members, 10 are predicted to be active proteases based on the sequence of their Zn binding catalytic sites (Black and White, *Curr. Opin. Cell. Biol* 10:654-659, 1998). The consensus catalytic sequence site based on ADAM and snake venom metalloproteases is HEXGHXXG^{*}XXHD (SEQ ID NO:51). The ADAM-TS family of proteins has homology to this consensus sequence except at the second conserved glycine. ADAMTS 9 has an asparagine at this conserved glycine site in the helix. Two other ADAM-TS proteins, ADAMTS-1 and ADAMTS-4, also have an asparagine in this position instead of glycine (Figure 32B). This suggests that ADAMTS-9, line ADAMTS-1 and ADAMTS-4, may have an active metalloprotease domain.

It has been proposed that an invariant cysteine residue in the pro-domain of MMP and ADAM proteins coordinates the catalytic Zn ion in the metalloprotease domain, thus maintaining the protease in an inactive state (Loechel et al., *J. Biol Chem.* 274:13427-33, 1999). Once the pro-domain is cleaved this interaction is interrupted and the protease is activated by a "cysteine switch" mechanism. A proposed cysteine switch

residue in ADAMTS-9 is marked in Figure 29 by a star. Proteolytic processing of the pro-domain of ADAM and ADAM-TS proteins is believed to occur by furin endopeptidases in the Golgi. ADAMTS-9 contains two potential furin cleavage sites (consensus RX(K/R)R; SEQ ID NO:35) at the end of the pro-domain (see Figure 29).

5 Based on the sequence of mature murine *ADAMTS-1*, the second furin cleavage site is most likely used in ADAMTS-9 (resulting amino-terminus FLSYPR).

Following the metalloprotease domain, ADAMTS-9 contains a cysteine-rich region that has homology to the disintegrin domain in snake venom metalloprotease and ADAMs. Next, all of the ADAM-TS family members contain an
10 internal TSP1 motif that has the two conserved heparin binding segments: W(S/G)XWSXW (SEQ ID NO:36) and CSVTCG (SEQ ID NO:37). Separating the internal TSP1 motif and the carboxy terminal TSP1-like submotifs is a variable length spacer region. As seen in Figure 32A, most ADAM-TS family members have between one and three TSP1-like submotifs at the end of the protein. However at the extremes
15 are ADAMTS 3 which has no TSP1-like motifs and *C. elegans* GON-1 which has 17 of these motifs. ADAMTS-9 contains one internal TSP1 motif and three TSP-1 like submotifs at the carboxyl end (Figure 30A). A possible role for ADAMTS 9 in the adult is suppression of angiogenesis through the carboxy-terminal TSP1 motifs.

Overall, the predicted mature forms of the ADAM-TS proteins show 20-
20 40% similarity to each other. Interestingly, by BLAST analysis ADAMTS-9 shows as much homology to *C. elegans* GON-1 as to other human ADAM-TS, suggesting that ADAMTS 9 may be the human homologue of GON-1. The dendrogram in Figure 30C (prepared with the MegAlign program (DNASar)) shows the relationship between the known human ADAM-TS members, ADAMTS 9, and GON-1.

25 The expression pattern of ADAMTS 9 was examined in a variety of human adult and fetal tissues using RT-PCR. For tissue distribution analysis, human multiple tissue cDNA panels I and II were purchased from Clontech. RT-PCR was performed using a touchdown procedure where the annealing temperature was dropped from 63°C to 57°C over 10 cycles then kept at 57°C for 20 cycles. The sense primer
30 was CAGGGGAAACAGACGATGACAACT (SEQ ID NO:38) and the antisense

primer was TGCGGTAACCCAAGCCACACT (SEQ ID NO:39). Expected product size was 510 bp. Control primers to glyceraldehyde-3-phosphate dehydrogenase (G3PDH) were supplied by Clontech--expected size is about 1 kb.

As seen with other ADAM-TS genes, Northern blot analysis showed very low levels of expression. Therefore a more sensitive RT-PCR procedure was used. The cDNA panels used were normalized to the mRNA expression levels of several different housekeeping genes to ensure accurate assessment of tissue specificity. ADAMTS-9 was found in ovary, pancreas, heart, kidney, lung, placenta, and strikingly in all fetal tissues examined (Figure 31), suggesting a possible role in development. In addition, using hybridization to cDNA libraries we have identified ADAMTS-9 in adult spinal cord and brain. However, ADAMTS-9 was not detected in colon, leukocyte, prostate, small intestine, testis, liver, skeletal muscle, spleen or thymus (Figure 31). Expression of the G3PDH housekeeping gene in all cDNAs tested is shown as a control for template integrity and the RT-PCR procedure. One notable difference in the expression pattern of ADAMTS-9 compared to other ADAMTS genes is the presence of ADAMTS-9 in the adult kidney. This is of interest since the chromosomal locus containing ADAMTS-9 is often deleted in renal tumors.

A genomic clone of ADAMTS 9 was obtained by screening a human P1 library and used for FISH analysis (Genome Systems). Briefly, the human ADAMTS-9 genomic clone was labeled with digoxigenin dUTP by nick translation. Labeled probe was combined with sheared human DNA and hybridized to normal metaphase chromosomes derived from PHA stimulated peripheral blood lymphocytes in a solution containing 50% formamide, 10% dextran sulfate and 2X SSC. Specific hybridization signals were detected by incubating the hybridized slides in fluoresceinated antidigoxigenin antibodies followed by counterstaining with DAPI for one-color experiments. Probe detection for two-color experiments was accomplished by incubating the slides in fluoresceinated antidigoxigenin antibodies and Texas red avidin followed by counterstaining with DAPI. A total of 80 metaphase cells were analyzed with 70 exhibiting specific labeling. Initial FISH experiments resulted in specific labeling of the short arm of chromosome 3. Measurement of 10 specifically labeled

chromosome 3's demonstrated that ADAMTS-9 is located at a position which is 30% the distance from the centromere to the telomere of chromosome arm 3p, an area which corresponds to 3p14.3-21.1 (Figures 32A and 32B). Since deletions and other rearrangements of this locus are frequent and early events in the pathogenesis of a number of human cancers (including renal cell carcinoma, breast cancers, uterine cervical carcinoma and vulvar carcinomas, this region may contain one or more tumor suppressor genes.

The chromosomal localization of the human ADAMTS 9 locus was independently confirmed by PCR analysis of the Stanford G3 radiation hybrid mapping panel. The G3 hybrid mapping panel (Stewart et al., *Genomic Res.* 7:422-433, 1997) containing 83 radiation hybrid DNA, as well as human and hamster control DNAs was obtained from Research genetics Inc. (Huntsville, Alabama). The human chromosome content of each somatic cell hybrid was established by the Stanford Human Genome Center using more than 10,000 STSs derived from random genetic markers and expressed tagged sequences (<http://www-shgc.stanford.edu/Mapping/rh/>). PCR reactions were carried out in a 10 µl reaction volume containing 25 ng DNA template, 25 µm deoxynucleotide triphosphates, 20 pmol of each oligonucleotide primer, 0.5 U of Taq polymerase (Boehringer Mannheim), 2.5 mM MgCl₂, 50 mM KCl and 10 mM Tris-HCl (pH 8.3). The sense primer is GTGCGCTGGGTCCCTAAATAC (SEQ ID NO:40) which is in the coding sequence and the antisense primer is AAAATCACAGGTTGGCAGCGG (SEQ ID NO:41) which is in an intronic sequence. Thirty cycles of PCR were performed. Ten cycles consisted of denaturing at 94°C for 15 seconds, annealing at 62°C for 30 seconds, going down 0.5°C each cycle and extension at 72°C for 30 seconds. Twenty more cycles were performed using the same denaturing and extension conditions and keeping the annealing at 57°C for 30 seconds. PCR was proceeded by a 2 min incubation at 94°C and followed by a 72°C final soak for 10 minutes. Amplified products were electrophoresed through a 2% agarose gel and visualized by ethidium bromide staining. The resulting PCR product was a 302 bp human specific fragment. The presence or absence of the ADAMTS 9 product was scored for each of the somatic cell hybrids. The results were submitted to the Stanford

Radiation Hybrid Server via the internet (<http://www-shgc.stanford.edu>) and the completed data were returned to us. ADAMTS 9 was linked to the ordered markers SHGC-33668 with a LOD score of 11.47 and SHGC-20118 (D3S3571) with a LOD score of 11.06. The results confirm localization of ADAMTS 9 to the short arm of chromosome 3 and place ADAMTS-9 within the context of established maps. Furthermore SHGC-20118 (D3S3571) has been mapped to 3p14.2, placing ADAMTS-9 closer to the 14.2-14.3 region of chromosome 3. This location is interesting in that it contains a well characterized breakpoint for translocations common in hereditary renal cell carcinomas.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polynucleotide that encodes an ADAMTS polypeptide, wherein the polypeptide comprises:
 - (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or
 - (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.
2. A polynucleotide according to claim 1, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.
3. A polynucleotide according to claim 1, wherein substitutions, if any, are present at no more than 5% of the consecutive residues of the ADAMTS protein.
4. A polynucleotide according to claim 1, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.
5. A recombinant expression vector comprising a polynucleotide according to claim 1.
6. A host cell transformed or transfected with an expression vector according to claim 5.
7. An isolated antisense polynucleotide complementary to at least 20 consecutive nucleotides present within a polynucleotide according to claim 1.

8. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and

(b) recovering an ADAMTS polypeptide.

9. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell according to claim 6 under conditions promoting expression of the polynucleotide; and

(b) recovering an ADAMTS polypeptide.

10. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

11. An ADAMTS polypeptide according to claim 10, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

12. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27.

13. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

14. An ADAMTS polypeptide according to claim 13, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

15. An ADAMTS polypeptide according to claim 13, wherein the polypeptide comprises at least 40 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

16. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

17. A pharmaceutical composition comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a physiologically acceptable carrier.

18. A vaccine comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a non-specific immune response enhancer.

19. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an ADAMTS polypeptide that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

20. A method for screening for an agent that modulates ADAMTS protein expression in a cell, comprising:

(a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein

substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) subsequently evaluating the effect of the candidate modulator on expression of an ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell.

21. A method for screening for an agent that modulates an ADAMTS protein activity, comprising:

(a) contacting a candidate modulator with an ADAMTS polypeptide, comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and

(b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

22. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neuroinflammation in a patient.

23. An agent according to claim 22, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

24. An agent according to claim 22, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

25. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neurodegeneration in a patient.

26. An agent according to claim 25, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

27. An agent according to claim 25, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

28. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for method for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration.

29. A composition according to claim 28, wherein the condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease and stroke.

30. A method for modulating ADAMTS activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS protein activity or expression, wherein the ADAMTS polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and thereby modulating ADAMTS activity in the cell.

31. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis.

32. A composition according to claim 31, wherein the condition is selected from the group consisting of cancer, arthritis and autoimmune diseases.

33. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with an invasive tumor.

34. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain tumor.

35. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20,

22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain injury.

36. An agent according to any one of claims 33-35, wherein the ADAMTS protein comprises a sequence recited in SEQ ID NO:16.

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AGGACCAAGCGGTTTGTGTCTGAGGCGCGCTTCGTGGAGACGCTGCTGGTGGCCGATGCGTCCATGGCTGCCTTCTACGG
GGCCGACCTGCAGAACCACATCCTGACGTTAATGTCTGTGGCAGCCGAATCTACAAGCACCCAGCATCAAGAATTCCA
TCAACCTGATGGTGGTAAAAGTCTGATCGTAGAAGATGAAAAATGGGGCCAGAGGTGTCCGACAATGGGGGGCTTACA
CTGCGTAACTTCTGCAACTGGCAGCGGCGTTTCAACCAGCCAGCGACCGGCACCCAGAGCACTACGACACGGCCATCCT
GCTCACCAGACAGAACTTCTGTGGGCAGGAGGGGCTGTGTGACACCCTGGGTGTGBCAGACATCGGGACCATTGTGACC
CCAACAAAAGCTGCTCCGTGATCGAGGATGAGGGGCTCCAGGCGGCCACACCCTGGCCCATGAACTAGGGCAGTCCTC
AGCATGCCCCAGCAGACTCCAAGCCCTGCACACGGCTCTTCGGGCCCATGGGCAAGCACCACTGATGGCACCCTGT
CGTCCACCTGAACCAGACGCTGCCCTGGTCCCCTGCAGCGCCATGTATCTCACAGAGCTTCTGGACGGCGGGACGGAG
ACTGTCTCCTGGATGCCCTGCTGCGGCCCTGCCCTCCCCACAGGCCCTCCGGGCCGATGGCCCTGTACCAGCTGGAC
CAGCAGTGCAGGCAGATCTTTGGGCCGATTTCGCCACTGCCCCAACACCTCTGCTCAGGACGTCTGCGCCAGCTTTG
GTGCCACACTGATGGGGCTGAGCCCTGTGCCACACGAAGAATGGCAGCCTGCCCTGGGTGACGGCACGCCGTGCGGGC
CTGGGCACCTCTGCTCAGAAGGCAGCTGTCTACCTGAGGAGGAAGTGGAGAGGCCCAAGCCCGTGGTAGATGGAGGCTGG
GCACCGTGGGGACCCTGGGGAGAATGTTCTCGGACCTGTGGAGGAGGAGTACAGTTTTACACCGTGAGTGCAAGGACCC
CGAGCCTCAGAATGGAGGAAGATACTGCCTGGGTGCGAGAGCCAAGTACCAGTCATGCCACACGGAGGAATGCCCCCTG
ACGGGAAAAGCTTCAGGGAGCAGCAGTGTGAGAAGTATAATGCCTACAATTACACTGACATGGACGGGAATCTCCTGCAG
TGGGTCCCCAAGTATGCTGGGGTGTCCCCCGGGACCGCTGCAAGTTGTTCTGCCGAGCCCGGGGAGGAGCGAGTTCAA
AGTGTTCGAGGCCAAGGTGATTGATGGCACCTGTGTGGGCCAGAAACACTGGCCATCTGTGTCCGTGGCCAGTGTGTCA
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CAACCACCAACATCACCCAGCCGCTGCTCCACGCACAGTGGGTGCTGGGGGACTGGTCTGAGTGTCTAGCACCTGCGGG
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TACCAGACAGGACGCCCGGAATTC

Fig. 1

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RTKRFVSEARFVETLLVADASMAAFYGADLQNHILTLMSVAARIYKHPSIKNSINLMVVKVLIVEDEKKGPEVSDNGGLT
LRNFCNWQRRFNQPSDRHPEHYDTAILLTRQNFCEGQEGLCDTLGVADIGTICDPNKSCSVIEDEGLQAAHTLAHELGHVL
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WVPKYAGVSPDRCKLFCRARGRSEFKVFEAKVIDGTLCGPETLAICVRGQCVKAGCDHVVDSEFWKLDKCGVCGGKGNSC
RKGSGSLTPTNYGYNDIVTIPAGATNIDVKQRSHPGVQNDGNYLALKTADGQYLLNGNLATSAIEQDILVKGTILKYSGS
IATLERLQSFRLPEPLTVQLLAVPGEVFPKVKYTFVPNDVDFSMQSSKERATTNITQPLLHAQWVLGDWSECSSTCG
AGWQRRTVECRDPSSGQASATCNKALKPEDAKPCESQLCPL.

Fig. 2

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CCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAATTCGGGGCCCCCACCCTGAACTTCTATAG
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Fig. 3A

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TGTACAAAGATTATCGGAACCTTCAATAAAAAAGCAAGGGTTATACTGACGTTGTGAGGATCCCTGAAGGAGCAACCCA
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 TGGAGTCACAGAGATGATTTTTTACATGGGATGGGCTATTAGCCACAAAGGAAATTCTGATTGTGCAGATCCTTGCAAC
 AGACCCAACTAAAGCATTAGACGTCGGTTACAGCTTTTTTGTCCCAAGAAGACCACTCAAAAAGTGAATTCCTGCAGCC
 CGGGGGATCCACTAGTTCTAGAGCGGCCG

Fig. 3B

MRLEWASLLLLLLLLCASCLALAADNPAAAPAQDKTRQPRAAAAAAQPDQRQWEETQERGLQPLARQRRSSGLVQNIDQ
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 TSSHGNWGSWGPWGQCSRSCGGGVQFAYRHCNNPAPRNSGRYCTGKRAIYRSCSVIPCPNGKSFREHQCEAKNGYQSDA
 KGVKTFVEWVPKYAGVLPADVCKLTCRAKGTGYVVVSPKVTDTGTECRPYSNSVCVRGRCVRTGCDGIIGSKLQYDKCGV
 CGGDNSSCTKIIGTFNKKSKGYTDVVRIPEGATHIKVRQFKAXDQTRFTAYLALKKKTGEYLINGKYMISTSETIINDING
 TVMNYSGWSHRDDFLHGMGYSATKEILIVQILATDPTKALDVRYSFVPPKTTQKVNCSGPDPLVLERP

Fig. 4

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KIAA0605 Accession #: AB011177

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Fig. 5A

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Fig. 5B

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 MELGPSQGETNEVCEQAGGACGPPRGKGFDRNVTGTPLTGDKDDEVDTHFASQEFFSANAISDQLLAGSOLKDFTLNETVNSIFAQAPRSS
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 POWEMSEWSECTAKGERSVVRDTRCSEDEKLCDPNTRPVGEKNCTGPPCDRQWTVSDWGPCSGSCGQGRTRHVVYCKTSDGRVVPESQCMETKPL
 AIHPCGDKNCPAHWLAQDWERCNTTCGRGVKKRLVLCMELANGKQTRSGPECLAKKPEESTCFERPCFKWYTSWPSECTKTCGVGVMRDVKCYQ
 GTDIVRGCDPLVKPVGRQACDLQPCPTEPPDDSCQDQPGTNALAIKVNLCGHWYYSKACCRSCRPPHS (951 amino acids)

Fig. 6

SUBSTITUTE SHEET (RULE 26)

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DNA sequence of metalloproteinase gene (KIAA0366) Accession #: AB002364

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Fig. 7A

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 agaaaaatat gttgtaaga ttgtgtgtg cgtctctga agcagaaaag ggactggaac 3900
 caattgtgca tatcagctga cttttgttt gtttagaaa agttacagta aaaattaaaa 3960
 agagatacca atggtttaca ctttaacaag aaattttgga tatggaacaa agaattctta 4020
 gactgtatt cctattatc tatattagaa atattgtatg agcaaatgg cagctgtgt 4080
 gtaataactg tatattgcaa aaatcagtat tatttaaga gatgtgtct caaatgattg 4140
 ttactatat tacatttctg gatgttctag gtgctgtcg ttgagtattg cctgtttga 4200
 catctatag gtaattttc aaagcagagt attacaaaag agaagttaga atiacagcta 4260
 ctgacaatat aaaggtttt gttgaatcaa caatgtgata cgtaaattat agaaaaagaa 4320
 aagaacaca aaagctatag atatacagat atcagcttac ctattgcctt ctatactat 4380
 aatttaagg attgtgtct tagtacactt gtggtcacag ggaatcaaga atagtaata 4440
 atgaactcgt gcaagacaaa actgaaaccc tctttccagg acctcagtag gcaccgttg 4500
 ggtgtcctt gttttgtgt gtgtgtgtt tttttaatt ttcgattgt tgacagatac 4560
 aaacagttat actcaatgta ctgtaataat cgcaaggaa aaagttttg gataacttat 4620
 ttgtatgtg gtagctgaga aaaatatcat cagtctagaa ttgatattg agtatagtag 4680
 agctttggg ctttgaagg aggttcaaga aagcatatgt cgtatgttga gatatttatt 4740
 ttccataggt tcatgttca aatgttaca accacaatgc atctgactgc aataatgtgc 4800
 taataattta tgtcagtagt caccttctc acagcaaagc cagaatgct ctctccagg 4860
 agtagatgta aagtactgt acatagaatt cagaactgaa gatatttatt aaaagttgat 4920
 tttttttct tgatagtatt tttatgtact aaatatttac actaatatca attacatatt 4980
 ttggtaaact agagagacat aattagagat gcatgctttg ttctgtgcat agagacctt 5040
 aagcaacta ctacagccaa ctcaaaagct aaactgaac aaatttgatg ttatgcaaac 5100
 atcttgcat tttagtagt gatattaagt tgatgacttg ttcccttca aggaacatt 5160

Fig. 7B

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aaattgtag gactcagcta gctgttcaat gaaattgtga attagaaaca tttttaaaag 5220
 tttttgaaag agataagtgc atcatgaati acatgtacat gagaggagat agtgatatca 5280
 gcataatgat tttgaggtca gtacctgagc tgtctaaaaa tatattatac aaactaaaat 5340
 gtagatgaat taacctctca aagcacagaa tgtgcaagaa cttttgcatt ttaatcgttg 5400
 taaactaaca gcttaaaacta ttgactctat acctctaaag aattgctgct actttgtgca 5460
 agaactttga aggtcaaat aggcataatc cagatagtaa aacaatccct aagccttaag 5520
 tctttttttt ttcttaaaaa ttcccataga ataaaattct ctctagtta cttgtgtgtg 5580
 catacatctc atccacaggg gaagataaag atggtcacac aaacagttc cataaagatg 5640
 tacataatca ttatacttct gacctttggg ctttcttttc tactaagcta aaaattcctt 5700
 tttatcaaa gtagacttac tgatgctgtt tgtgtactg agagcacgta ccaataaaaa 5760
 tgtaacaaa atai 5774

Fig. 7C

1
 slwliaaalvevrt sadgqagneemvqidlpikryreyelvtpvstnlegrylshtlsashkksardvssnpeqlffni
 tafgkdfhlrlkptqlvapavvewhetslvpgnitdpinnhpgsatyrirkteplqtncaayvgdivdipgtsvaisn
 cdglagmiksdneeyfieplergkmeekgrihvvykrsaveqapidmskdfhyresdleglddltvygnihqqlnet
 mrrrrhagendynievlvgddsvvrfhgkehvqnylltlnmivnei yhdeslgvhinvlvrmlgyaksisliern
 psrslenvcrwasqqrsdlnhsehdhai fltrqdfgpagmqgyapvtgmchpvrsc tlnhedgfssafvvahtghvl
 gmedhgqgnrcgdetamgsvmaplvqaafhryhwsrscgqelkryihsydc lldpfdhdwpk lpe lpginysmdeqcrf
 dfvgvykmctaftrtdpckqlweshp dnp yfcktkk gpldgt ecaagkwcykghcmwkn anqqkqdg nwgswtkfgscs
 rtcgtgvrfrtrqcnnmpingggdcpgvnfeyqlcnte ecqkhfed fraqqcqrnshfeyqntkhhw lpyehdpkkr
 chlycsketgdvaymkqlvhdgthcsykdpsicvrgecvkvgcdkeignkvedkcgvcggdnshcrtvkgtftrtp
 klgy lkmfdippgarhvl iqedeasphilaiknqatghy l ngkgeeaksr t f idlgvewdynieddies lhtdgp l hdp
 vivliipqendrssltykiihedsvptinsnnviqueeldtfewalkswsqvskpcgggfytkygcrrksdnkmvhrs
 fceankpkpirmcniquecthlwvaeewehctkcgssgyqlrtvrclqplldgt nrsvhskycmgrp esrrpcnrv
 pcpaqwk tgpwsecsvt cgegtevrql cragdhcdgkpesvracqlppcndepclgdksifcmevlarycsipgynk
 lccescskrsstlpppyllaaethddvisnpsdlprslvmptslvpyhsetpakkmslssissvggnayaafrpnskp
 dganlgrsaqqagsktvrlvtvpsspptkrvhlssasqmaasffaasdsigassqartskkdgkiidnrrptsstle
 r (1,201)

80

Fig. 8

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GGAATTGCGGGCCGCGTCGACGTCAATACCAACTCCGAGCACACGGCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCAC
ATTCCGGTCTCATGATGGGGATTATTTTATTGAACCACTACAGTCTATGGATGAACAAGAAGATGAAGAGGAACAAAACA
AACCCACATCATTATAGGCGCAGCGCCCCCAGAGAGAGCCCTCAACAGGAAGGCATGCATGTGACACCTCAGAACAC
AAAAATAGGCACAGTAAAGACAAGAAGAAAACCAGAGCAAGAAAATGGGGAGAAAGGATTAACCTGGCTGGTGACGTAGC
AGCATTAAACAGCGGCTTAGCAACAGAGGCATTTTCTGCTTATGGTAATAAGACGGACAACACAAGAGAAAAGAGGACCC
ACAGAAGGACAAAACGTTTTTATCCTATCCACGGTTTGTAGAAGTCTTGGTGGTGGCAGACAACAGAATGGTTTCATAC
CATGGAGAAAACCTTCAACACTATATTTAACTTTAATGTCAATTGATGGGCCTTCCATATCTTTAATGCTCAGACAAC
ATTAAAAACCTTTGCCAGTGGCAGCATTGAAGAACAGTCCAGGTGGAATCCATCATGATACTGCTGTTCTCTTAACAA
GACAGGATATCTGCAGAGCTCAGACAAATGTGATACCTTAGGCCTGGCTGAACCTGGGAACCATTTGTGATCCCTATAGA
AGCTGTTCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTTACGATCGCCCATGAGCTGGGCCATGTGTTAACATGCC
TCATGATGACAACAACAAATGTAAGAAGAAGGAGTTAAGAGTCCCAGCATGTCATGGCTCCAACACTGAACCTCTACA
CCAACCCCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCACTGAGTTTTAGACACTGGTTATGGCGAGTGTGCTT
AACGAACCTGAATCCAGACCCCTACCCCTTGCCTGTCCAACCTGCCAGGCATCCTTTACAACGTGAATAACAATGTGAATT
GATTTTTGGACCAGGTTCTCAGGTGTGCCCATATATGATGCAGTGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTAC
ACAAAGGCTGCCGACTCAGCACACCCCTGGGCCGATGGGACGGAGTGCAGCCTGGAAAGCACTGCAAGTATGGATT
TGTGTTCCCAAAGAAATGGATGTCCCGTGACAGATGGATCCTGGGGAAGTTGGAGTCCCTTTGGAACCTGCTCCAGAAC
ATGTGGAGGGGGCATCAAACAGCCATTCGAGAGTGCAACAGACCAGAACCAAAAATGGTGGAATACTGTGTAGGAC
GTAGAATGAAATTTAAGTCTGCAACACGGAGCCATGTCTCAAGCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCAC
TTTGACGGGAAGCATTTTAACATCAACGGTCTGCTTCCCAATGTGCGCTGGGTCCTAAATACAGTGGAATCTGATGAA
GGACCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACACAGCCTACTATCAGCTTCGAGACAGAGTGATAGATGGAACCTC
CTTGTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTGCCGGCAAGCTGGATGCGATCATGTTTTAACTCAAAA
GCCCCGAGAGATAAATGTGGGGTTTGTGGTGGCGATAATCTTCATGCAAAACAGTGGCAGGAACATTTAATACAGTACA
TTATGGTTACAATACTGTGGTCCGAATTCAGCTGGTGTACCAATATTGATGTGCGGCAGCACAGTTTCTCAGGGGAAA
CAGACGATGACAACACTTAGCTTTATCAAGCAGTAAAGGTGAATCTTGCTAAATGGAACTTTGTTGTCAATGGCC
AAAAGGGAATTCGCATTGGGAATGCTGTGGTAGAGTACAGTGGGTCCGAGACTGCCGTAGAAAGAATTAACCTAACAGA
TCGCATTGAGCAAGAACCTTTGCTTCAGGTTTTGTGCGTGGGAAAGTTGTACAACCCGATGTACGCTATTCTTTCAATA
TTCCAATTGAAGATAAACCTCAGCAGTTTTACTGGAACAGTCAATGGGCATGGCAAGCATGCAGTAAACCTGCCAAGGG
GAACGGAAACGAAAACCTGTTTGCACCAGGGAATCTGATCAGCTTACTGTTTCTGATCAAAGATGCGATCGGCTGCCCA
GCCTGGACACATTACTGAACCTGTGGTACAGACTGTGACCTGAGGTGGCATGTTGCCAGCAGGAGTGAATGTAGTGCCC

Fig. 9A

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AGTGTGGCTTGGGTTACCGCACATTGGACATCTACTGTGCCAAATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGAT
 GATGGTTTTTGCAGCAGCCATCCCAAACCAAGCAACCGTGAAAAATGCTCAGGGGAATGTAACACGGGTGGCTGGCGCTA
 TTCTGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACCCAGAGGAGAAGGGCTATTTGTGTCAATACCCGAAATG
 ATGTACTGGATGACAGCAAATGCACACATCAAGAGAAAAGTTACCATTGAGAGGTGCAGTGAGTTCCTTGTCCACAGTGG
 AAATCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGGAAAAGGGCATAAGCACCGCCAGGTCTGGTGTGAGTTTGGTGA
 AGATCGATTAAATGATAGAATGTGTGACCCAGAGGTGACGCGGCCGGAATTCGCGCGATACTGACGGGCTCCAGGAGT
 CGTCGCCACCAATCCCATATGGAAACCGTCGATATTCAGCCATGTGCCTTCAAGCCGAATTCAG

Fig. 9B

GIRGRVDVNTNSEHTAVISLCSGMLGTFRSHDGDYFIEPLQSMDEQEDEEEQNKPHIYRRSAPQREPSTGRHACDTSEH
 KNRHSDKKKTRARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNTRKTRHRRTKRFLSYPRFVEVLVADNRMVSY
 HGENLQHYILTLMSIDGPSISFNAQTTLNLCQWQHSKNSPGGIHHD TAVLLTRQDICRAHDKCDTLGLAELGTICDPYR
 SCSISEDSGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPMWSKCSRKYITEFLDTGYGECCL
 NEPESRPYPLPVQLPGILYNVNKQCELI FGPGSQVC PYMMQCRRLWCNNVNGVHKGCRTQHTPWADGTECEPGKHCKYGF
 CVPKEMDVPVTDGSGWSWSPFGTCSRTCGGGIKTAIRECNRPKNGGKYCVGRRMKFKSCNTEPCLKQKRDFRDEQCAH
 FDGKHFNINGLLPNVRWVPKYSILMKDRCKLFCRVAGNTAYYQLRDRVIDGTGCGQDNDICVQGLCRQAGCDHVLNSK
 ARRDKCGVCGGDNSCKTVAGTFNTVHYGYNTVVRIPAGATNIDVRQHSFSGETDDDNYLALSSSKGEFLNGNFVVTMA
 KREIRIGNAVVEYSGETAVERINSTDRIEQELLLQVLSVGKLYNPDVRYSFNIPIEDKPPQFYWNHGPWQACSKPCQG
 ERKRKL VCTRESQDLTVSDQRCDRLPQPGHITEPCGTDCDLRWHVASRSECSAQCGLYRTLDIYCAKYSRLDGKTEKVD
 DGFCSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRRAICVNTRNDVLDDSKCTHQEKVTIQRCEFPQPW
 KSGDWSECLVTCGKGHKHRQVWCQFGEDRLNDRMCDPEVDAAANSADTDGLQESSPPPIIWKPSIFSHVPSSRIP

Fig. 10

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cacatatgcacgagagagacagaggagaaagagacagagacaaaggcacagcggaagaaggcagagacagggcaggcac
agaagcgggccagacagagtcctacagagggagagggcagagaagctgcagaagacacaggcagggagagacaaagatcc
aggaaaggagggctcaggagagagtttgagaagccagaccctgggcacctctccaagccaaggactaagttttct
ccatttcctttaacggtcctcagcccttctgaaaactttgcctctgaccttggcaggagtccaagccccaggctacaga
gaggagctttccaaagctaggggtgtggaggacttggcgccctagacggcctcagtcctcccagctgcagtaccagtgcc
atgtcccagacaggctcgcatcccgaggagggttggcagggcgctggctgtgggagcccaaccctgcctcctgtctccc
cattgtgcgctctcctggctgggtgtggctgtcttgcactgtggcctctctcctgccctcagcccggctggccagcc
ccctccccgggagggagagatcgtgtttccagagaagctcaacggcagcgtcctgcctggctcgggcacccctgccagg
ctgttgtgccgcttgaggcctttggggagacgctgctactagagctggagcaggactccggtgtgcaggtcgaggggct
gacagtgcagtacctgggccaggcgctgagctgtgggtggagcagagcctggcacctacctgactggcaccatcaatg
gagatccggagtcggtggcatctctgcactgggatgggggagccctgttaggcgtgttacaatatcggggggctgaactc
cacctccagccctggagggaggcaccctaactctgctgggggacctggggctcacatcctacgccggaagagtcctgc
cagcggcgaaggtcccatgtgcaacgtcaaggctcctcttgaagccccagccccagaccccaagagccaagcgcttg
cttcactgagtagattttgagacactgggtggcagatgacaagatggccgattccacggtgcgggctaaagcgc
tacctgctaacagtgatggcagcagcagccaaggccttaagcacccaagcatccgaatcctgtcagcttgggtggac
tcggctagtgatcctgggctcaggcgaggagggggccccaagtggggccagtgctgccagaccctgcgcagcttctgtg
cctggcagcggggcctcaacaccctgaggactcggaccctgaccactttgacacagccattctgtttaccgctcaggac
ctgtgtggagtctccacttgcgacacgctgggtatggctgatgtgggcaccgtctgtgaccggctcggagctgtgccat
tgtggaggatgatgggctccagtcagccttactgtgctcatgaactgggtcatgtcttcaacatgctccatgacaact
ccaagccatgcatcagttgaaatgggcctttgagcacctctcgccatgtcatggcccctgtgatggctcatgtggatcct
gaggagccctggtccccctgcagtggccgcttcatcactgacttcttgacaatggctatgggcactgtctcttagacaa
accagaggctccattgcatctgcctgtgactttccctggcaaggactatgatgctgaccgccagtgccagctgaccttg
ggcccgactcacgccattgtccacagctgccgcccctgtgctgccctctgggtgctctggccacctcaatggccatgcc
atgtgccagaccaaactcggcctgggcccagtgccacaccctgcggggccgcacaggcctgcatgggtggctcgtgcct
ccacatggaccagctccaggacttcaatattccacaggtgggtggctggggtccttggggaccatggggtgactgtctc
ggacctgtgggggtgggtccagttctcctcccagactgcacgaggcctgtcccccggaatgggtggcaagtactgtgag
ggccgccgtaccgcttccgctcctgcaacactgaggactgcccactggctcagccctgaccttccgcgaggagcagtg
tgctgcctacaaccaccgcaccgacctcttcaagagcttcccagggcccatggactgggttctcgtacacaggcggtg
ccccccaggaccagtgcaaaactcacctgccagggccggcactgggctactactatgtgctggagccacgggtggtagat

Fig. 11A

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gggacccccctgttccccggacagctcctcggtctgtgtccagggccgatgcatccatgctggctgtgatcgcatcattgg
ctccaagaagaagtttgacaagtgcattggtgtgcggaggggacggttctggttgagcaagcagtcaggctccttcagga
aattcaggtacggatacaacaatgtggtcactatccccgcggggccaccacattcttgtccggcagcagggaaccct
ggccaccggagcatctacttggccctgaagctgccagatggctcctatgccctcaatggtgaatacacgctgatgccctc
ccccacagatgtggtactgcctggggcagtcagcttgcgtacagcggggccactgcagcctcagagacactgtcaggcc
atggggcactggcccagcctttgacactgcaagtcctagtggctggcaacccccaggacacacgcctccgatacagcttc
ttcgtgccccggccgaccccttcaacgccacgccccactccccaggactggctgcaccgaagagcacagattctggagat
ccttcggcggcgcccctggcgggcaggaaataacctcactatccccggctgccctttctgggcaccggggcctcgactt
agctgggagaaagagagagcttctgttgcctcatgctaagactcagtgggaggggctgtggcgtagacctgcc
ctcctctctgccctaatgcgcaggctggccctgccctggtttcctgccctgggaggcagtgatgggttagtggaaggaa
gggctgacagacagccctccatctaaactgccccctctgccctgcgggtcacaggagggaggggaaggcaggagggcc
tgggccccagttgtaattatttagtatttattcacttttatttagcaccagggaggggacaaggactagggtcctggg
aacctgacccctgacccctcatagccctcaccctggggctaggaaatccagggtggtggtgataggatataagtgggtgt
gtatgcgtgtgtgtgtgtgtgaaatgtgtgtgtgcttatgtatgaggtacaacctgttctgctttcctcttctgaa
ttttattttttgggaaaaaagaagtcaagggtagggtgggccttcaggagtgaggattatcttttttttttttcttt
ctttctttcttttttttttttgagacagaatctcgctctgtcgccaggctggagtgaatggcacaatctcggtcact
gcctcctccgctcccggttcaagtgattctcatgcctcagcctcctgagtagctgggattacaggctcctgccaccac
gccagctaatttttgttttgttttgttttgagacagagtcctcgctattgtcaccagggtggaatgatttcagctcact
gcaaccttcgccacctgggttcagcaattctcctgcctcagcctcccgagtagctgagattataggcacctaccaccac
ggccggctaatttttgtatttttagtagagacgggtttcaccatgttgccaggctggtctcgaactcctgacctagg
tgatccactcgcttcatctcccaaagtgtgggattacaggcgtgagccaccgtgcctggccacgcccactaattttt
gtatttttagtagagacagggtttcaccatgttgccaggctgctcttgaactcctgacctcaggtaatcgacctgcctc
ggccccccaaagtgtgggattacagggtgtgagccaccacggcggtacatattttttaaattgaattctactatttatg
tgatccttttggagtcagacagatgtggttgcatcctaactccatgtctctgagcattagatttctcatttgccaataat
aatacctcccttagaagttgtgtgaggattaaataatgtaataaagaactagcataac

Fig. 11B

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MSQTGSHPGRGLAGRWLWGAQPCLLLPVPLSWLVLLLLLLASLLPSARLASPLPREEEIVFPEKLNGSVLPGSGTPAR
LLCRLQAFGETLLLLLEQDSGVQVEGLTVQYLGQAPPELLGGAEPGYLTGTINGDPESVASLHWDGGALLGVLQYRGAEL
HLQPLEGGTPNSAGGPGAHLRRKSPASGGQGPCNVKAPLGSPSPRRRAKRFASLSRFVETLVVADDKMAAFHGAGLKR
YLLTVMAAAAKAFKHPSIRNPVSLVTRLVILGSGEEGPQVGPSAAQTLRSFCAWQRLNTPEDSDPDHFDTAILFTRQD
LCGVSTCDTLGMADVGTCDPARSCAIVEDDGLQSAFTAHELGHVFNMLHDNSKPCISLNGPLSTRHVMAFVMAHVDP
EEPWSPCSARFITDFLDNGYGHCLLDKPEAPLHLPVTFPGKDYDADRQCQLTFGPDSRHCPQLPPCAALWCSGHLNGHA
MCQTKHSPWADGTPCGPAQACMGGRCLEMDQLQDFNIPOAGGWGPWGPWGDCSRTC GGGVQFSSRDCTRPVPRNGGKYCE
GRRTRFRSCNTEDCPTGSALTFREEQCAAYNHRTDLFKSFGPMDWVPRYTGVAPQDQCKLTCQARALGYYYVLEPRVVD
GTPCSPDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGDGGSGCSKQSGSFRKFRYGYNVVTIPAGATHILVRQQGNP
GHRSIYLALKLPDGSYALNGEYTLMPSPTDVVLPGAVSLRYSGATAASETLSGHGPLAQPLTLQVLVAGNPQDTRLRYSF
FVPRPTPSTPRPTQDWLHRRQAQILEILRRRPWAGRK

Fig. 12

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Rat ADAMTS 5 DNA

ACTCACTATA GGGCTCGAGC GGCCGCCCGG GCAGGTCAGA GGCTCACTGG CAGCTCTCTA	60
GACCTGCGAC GCTGCTTCTA TTCCGGGTAT GTGAACGCGG AGCCAGACTC CTTTGCTGCT	120
GTAAGCCTAT GCGGGGTCT CCGCGGAGCC TTTGGCTACC AAGGTGCGGA GTATGTCATT	180
AGCCCTCTGC CCAACACCAG CGCGCCTGAG GCGCAGCGTC ATAGCCAGGG CGCACACCTT	240
CTCCAGCGCC GGGGTGCTCC CGTAGGGCCT TCCGGAGACC CTACCTCTCG CTGCGGGGTG	300
GCCTCGGGCT GGAACCCCGC CATCCTGAGG GCCTTGAGCC CTTATAAACC ACGGCGGACG	360
GGCGTGGGCG AAAGCCACAA CCGGCGCAGG TCTGGGCGCG CCAAGCGCTT CGTGTCTATA	420
CCACGGTACG TGGAGACACT GGTGGTGGCG GACGAGTCAA TGGTCAAGTT TCACGGCGCG	480
GATTTGGAAC ATTATCTGCT GACGCTGCTG GCCACGGCGG CGCGACTCTA CCGCCACCCC	540
AGCATCTCA ACCCTATCAA CATCGTTGTG GTCAAGGTGT TACTCTTAGG AGATCGTGAC	600
ACTGGGCCCC AGGTACAGG CAACGCGGCC CTGACTCTGC GCAACTTCTG TGCCTGGCAG	660
AAAAAGTTGA ACAAAGTGAG CGACAAGCAC CCCGAGTACT GGGACACAGC CATCCTCTTC	720
ACCAGACAGG ACCTATGCGG GGCTACCACC TGTGACACCT TGGGCATGGC TGATGTGGGC	780
ACCATGTGTG ATCCCAAGAG AAGCTGCTCT GTCATCGAGG ACGATGGGCT TCCGTCGGCC	840
TTCACCACTG CCCATGAGCT GGGCCATGTG TTCAACATGC CCCATGACAA CGTGAAGGTG	900
TGTGAGGAGG TGTTTGGGAA GCTCAGAGCC AACCACATGA TGTCTCCGAC ACTCATCCAG	960
ATCGACCGTG CCAACCCCTG GTCAGCCTGC AGTGCTGCCA TTATCACCGA CTTCTTGAC	1020
AGCGGGCAGG GTGACTGCCT CCTGGACCAG CCCAGCAAGC CCATCACCTT GCCTGAGGAC	1080
CTGCCAGGCA CAAGCTACAG TTTGAGCCAA CAGTGCGAGC TGGCCTTTGG GGTGGGCTCT	1140
AAGCCCTGCC CATATATGCA GTACTGTACA AAGCTGTGGT GCACCGGCAA GGCCAAGGGG	1200
CAGATGGTGT GCCAGACTCG CCACTTCCCC TGGGCAGATG GCACCAGCTG TGGTGAGGGC	1260
AAGTTCTGCC TCAAGGGAGC CTGCGTGGAG AGACACAACC CAAACAAGTA CCGGGTGGAC	1320
GGCCCTTGGG CCAAGTGGGA GCCTTATGGT CCCTGCTCGC GCACCTGCGG TGGGGGCGCG	1380
CAGCTGGCCC GGAGGCAAGT GCAAGCAACC CTACCCCTGC CAACGGGCGG GAAGTACTGC	1440
GAGGGAGTGA GAGTGAAATA CCGATCTTGC AACTTGGAGC CCTGCCCCAG CTCAGCCTCT	1500
GGCAAGAGCT TCCGGGAA	1518

Fig. 13

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THYRARAARAGQRLTGSSDLRRCFYSGYVNAEPDSFAAVSLCGGLRGAFGYQGAEYVISPLNNTSAPEAQRHSQGAHL
 LQRRGAPVGPSPDPTSRGVSAGWNPAILRALDPYKPRRTGVGESHNRSSGRAKRFVSIPTYVETLVVADESMVKFHGA
 DLEHYLLTLATAARLYRHSILNPIINIVVKVLLGDRDTGPKVTGNAALTLRNFCAWQKLNKVS DKHPEYWDTAILF
 TRQDLGATTCDTLGMAADVGTMCDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVC EEVFGKLRANHMMSPILQ
 IDRANPWSACSAAIITDFLD SGHGDCLLDQPSKPITLPEDLPGTSYSLSQCELAFGVGSKPCPYMQYCTKLWCTGKAKG
 QMVCQTRHFPWADGTSCGEGKFLKGACVERHNPNKYRVDGPWAKWEPYGPCSRTC GGGAQLARRQVQATLPLPTGGKYC
 EGV RVKYRSCNLEPCPSSASGKSFR

Fig. 14

GATGCATCTAAGCCCTGGTCCAAATGCACTTCAGCCACCATCACAGAATTCCTGGATGATGGCCATGGTAACGTGTTGCT
 GGACCTACCACGAAAGCAGATCCTGGGCCCCGAAGAACTCCAGGACAGACCTACGATGCCACCCAGCAGTGCAACCTTA
 CATTGGGCTGAGTACTCCGTGTGTCCCGCATGGATGTCTGTGCTCCCCTGTGGTGTGCTGTGGTACGCCAGGGCCAG
 ATGGTCTGTCTGACCAAGAAGCTTCTGCGGTGGAAGGGACGCCTTGTTGAAAGGGGAGAATCTGCCTGCAGGGCAAATG
 TGTGGACAAAACCAAGAAAAATATTATTCAACGTCAAGCCATGGCAACTGGGGATCTTGGGGATCCTGGGGCCAGTGTT
 CTCGCTCATGTGGAGGAGGAGTGCAGTTTGCTATCGTGTGTAATAACCTGCTCCCAGAAACAACGGACGCTACTGC
 ACAGGGAAGAGGGCCATCTACCGCTCCTGCAGTCTCATGCCCTGCCACCCAAATGGTAAATCATTTGTCATGAACAGTG
 TGAGGCCAAAAATGGCTATCAGTCTGATGCAAAAGGAGTCAAACTTTTGTGGAATGGGTCCCAAATATGCAAGTGCC
 TGCCAGCGATGTGTGCAAGCTGACCTGCAGAGCCAAAGGGACTGGCTACTATGTGGTATTTCTCCAAAGGTGACCGAT
 GGCATGAATGTAGCCGTACAGTAATTCGCTGTGCGTCCGGGGGAAGTGTGTGAGAACTGGCTGTGACGGCATATTGG
 CTCAAAGCTGCAGTATGACAAGTGCGGAGTATGTGGAGGAGACAACCTCAGCTGTACAAAGATTGTTGGAACCTTTAATA
 AGAAAAGTAAGGGTTCANCTGACGTGGTGAGGATTCCTGAAGGGGCAACCCACATAAAAGTTCGACAGTTCAAAGCCAAA
 GACCAGACTAGATTCAGTCTATTTAGCCCTGAAAAAGAAAAACGGTGAGTACCTTATCAATGGAAGTACATGATCTC
 CACTTCAGAGACTATCATTGACATCAATGGAACAGTCATGAACTATAGCGGTTGGAGCCACAGGGATGACTTCCTGCATG
 GCATGGGCTACTCTGCCACGAAGGAAATTCTAATAGTGCAATTCTTGCAACAGACCCCACTAAACCATTAGATGTCCGT
 TATAGCTTTTTTGTCCCAAGAGTCCACTCCAAAAGTAACTCTGTCACTAGTCATGGCAGCAATAAAGTGGGATCACA
 CACTTCGACGCCGAGTGGGTCACGGGCCATGGCTCGCTGCTCTAGGACCTGTGACACAGGTTGGCACACCAGAACGG
 TGCAGTGCCAGGATGGAACCGGAAGTTAGCAAAAGGATGTCTCTCTCCAAAGGCCTTCTGCGTTTAAGCAATGCTTG
 TTGAAGAAATGTTAG

Fig. 15

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DASKPWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVCPGMDVCAPLWCAVVRQGQ
MVCLTKKLPAVEGTPCGKGRICLOGKCVDTKKKYYSTSSHGNWGSWSWGQCSRSCGGGVQFAYRRCNNPAPRNNGRYC
TGKRAIYRSCSLMPCPPNGKSRHEQCEAKNGYQSDAKGVKTFVEWVPKYASVLPDVCCLTCRAKGTGYVVFSPKVD
GTECRPYSNSVCVRGKCVRTGCDGIIGSKLQYDKCGVCGGDNSSCTKIVGTFNKKSXGSDVVRIPGATHIKVRQFKAK
DQTRFTAYLALKKKNGEYLINGKYMISTSETIIDINGTMNYSWGSRRDDFLHGMGYSATKEILIVQILATDPTKPLDVR
YSFFVPKKSTPKVNSVTSHGSNKVGSHTSQPQWVTGPWLACSRCTDGTGWHTRTVQCQDGNRKLAKGCPLSQRPSAFKQCL
LKKC

Fig. 16

18/39

M - - - - -		Majority			
		10	20	30	40
1	M - - - - - G D V Q - R A A R S - - - - - R G S L S A H M L	mADAMTS-1			
1	- - - - -	hADAMTS-2			
1	- - G I R - - - - -	hADAMTS-3			
1	L L G A R O Y R R N S G P P T P A P E T S I A N S K H P A R L S R A A P P G A Q	rADAMTS-4			
1	M - - - - - S Q T G S H P G R G L A G R - - - - W L W G A Q P C L L L	KIAA0688			
1	S L - - - - -	KIAA0366			
1	M D G R W Q C S - - - - -	KIAA0605			
- - - - - L L L L A L - T V L L S A D - - A G - P - - - E E E L		Majority			
		50	60	70	80
20	- - - - - L L L L A S I T M L L C A R G A H G R P T E E D E E L	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - -	hADAMTS-3			
41	R T M R L E W A S L L L L L L L C A S C L A L A A D N P A A A P A Q D K T R Q	rADAMTS-4			
27	P I V P L S W - - - L V W L L L L L L A S L L P S A R - - L A S P L P R E E E I	KIAA0688			
3	- - - - - W L I A A A L V E V R T S A D G Q A G N E E M V Q I D L	KIAA0366			
9	- - - - - C W A W F L L V L A V V A G D T V S T G S T D N S P T S N S L E G G T	KIAA0605			
V - - - - P - - - - - L R G - - - P - G - - G T T S R L -		Majority			
		90	100	110	120
47	V L - - - P S - - - - - L E R A - - - P - G H D S T T T R L -	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - -	hADAMTS-3			
81	P R - - - A A A A A Q P D Q R Q W E E T Q E R G H L Q P L A R Q R R S S G L V	rADAMTS-4			
62	V F - - - P E - - - - - K L N G S V L P - G - S G T P A R L L	KIAA0688			
31	P I K R Y R E Y E L V T P V S T N L E G R Y L S H T L S A S H K K R S A R D V S	KIAA0366			
44	D A T A F W - - - - - W G E W T K W T A F S R S C G G G V T S Q E R	KIAA0605			
- N L D - - - - - G - - - - L - L E R D S G V - A P G - -		Majority			
		130	140	150	160
65	- R L D A F - - - - - G Q Q L H L K L Q P D S G F L A P G F T	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - - G R V D - - - - -	hADAMTS-3			
118	Q N I D Q L Y S G G G K V G Y L V Y A G G R R F L L D L E R D D T V G A A G G I	rADAMTS-4			
83	C R L Q A F - - - - - G E T L L L E L E Q D S G V Q V E G L T	KIAA0688			
71	S N P E Q L F - - - - - F N I T A F G K D F H L R L K P N T Q L V A P G A V	KIAA0366			
73	H C L Q - - - - - Q R R K S V P G P G - -	KIAA0605			

Fig. 17A

	V Q	- - T G L S P	- - - - -	G A	- - - - - H C P	Majority
		170	180	190	200	
90	L Q	- - TVGRSPGSEAGHL D	- - PTGD	- - LAHCF	mADAMTS-1	
1	-	- - - - -	- - - - -	- - - - -	hADAMTS-2	
8	-	- - - - -	- - - - -	- - - - -	hADAMTS-3	
158	V T	- - AGGLSASS	- - GH	- - RGHC F	rADAMTS-4	
109	V Q	- - YLGQAP	- - ELLG	- - GA	KIAA0688	
104	V EWHETSLVPGNITDPI NNHQPGSATYRIRKTEPLQT NCA	KIAA0366				
87	- NRTCTGT SKRYQLCRVQECP PDGRSFREEQC VSFNSHVY	KIAA0605				
	Y	- GTVN GD PG SXAA LS LC GG	- LLGX F	- XVDGA EYFIE PL	Majority	
		210	220	230	240	
115	YSGT VN GD PGSAAA LS LCEG	- VRGA F	- YLQGEEFFI QPA	mADAMTS-1		
1	-	- - - - -	- - - - -	- - - - -	hADAMTS-2	
8	- - - - VNTN SEHTAVISLC SG	- MLGT F	- RSHDG DYFI EPL	hADAMTS-3		
175	YRGTV DG SP RS LAVFDLC GG	- LDGF F	- AVKHARYTL RP L	rADAMTS-4		
128	LTGT IN GD PESVAS LHWDGG ALLGV L	- QYRGAEL HLQP	- KIAA0688			
144	YVGDI VD IPG TSVA ISNC DG	- LAGMI	- KSDNEEY FI EPL	KIAA0366		
126	N GRTHQWKPLYPDDY VH ISSKPCDL HC TTVDGQRQLM VP A	KIAA0605				
	- - - - - LE	- GRPX EE GG	- RP	- Y-R	- - - - H-LRRR-P	Majority
		250	260	270	280	
152	P GVATER LAPAVPEEEEESS ARP	- - - - - QFHILRRRRR	mADAMTS-1			
1	-	- - - - -	- - - - -	- - - - -	hADAMTS-2	
41	QSMD	- - EQED EEEQNKP HI IYRSSA	- - PQREP	hADAMTS-3		
212	--LRGS WAESERVYG DG SSRI LHVTREG FSFEALPP RTS	rADAMTS-4				
165	- - - - - LEGGP NSAGG	- P	- - GAHIL RRKS P	KIAA0688		
181	- - - - - ER GKQMEEE KGRI HVVYKRSA	- - - - -	- - KIAA0366			
166	R DGTSC KL TD LRGV CVSGK CEPI GC DGVLFS TH TL DKCG I	KIAA0605				
	C SG-GA-CGVVE--PLHS SS-RPT-	- - - - -	Majority			
		290	300	310	320	
183	G SG-GAK CGVMDETLP TS DS RP ESQNTRNQW	- - - - - mADAMTS-1				
1	-	- - - - - hADAMTS-2				
69	S TGRHA-CDTSE HKNR HS KD KKKT RARKWG ERINLAGD VA	hADAMTS-3				
250	C ET PASPSGAQESP SVHSSSR RT EL APQ	rADAMTS-4				
187	A SGQ GP MCNVKA-PLGPS PRPR	- - - - - KIAA0688				
202	- - - - - VEQA PIDMSKD FH YRES DL EGLDDL GTVYG	KIAA0366				
206	C QGD GS SCT HT VT	- - - - - KIAA0605				

SUBSTITUTE SHEET (RULE 26)

----- GLAHT - - S - - - - - - - - - - RRTKRFFASEARF -		Majority
	330 340 350 360	
214	---PVRDPTPODAGKPSGPGS-----IRKKRFVSSPRY-	mADAMTS-1
1	-----RTKRFFVSEARF-	hADAMTS-2
108	ALNSGLATEAFSA YGNKTDN TREKRTHRRRTKRFLSYPRF-	hADAMTS-3
279	---LLDHSAFSPAGNAGPQTK---WRRRRRSISRARQ-	rADAMTS-4
209	-----RAKRFFASLSRF-	KIAA0688
232	NIHQQLNET-----MRRRRRHAGENDYN	KIAA0366
219	NYRKGN AHLGYSLVTHIPAGARDIQIVERKK-----S	KIAA0605
VEVLLVADDSMAAFHGAG-LQNYLLTLM SIAARIYKHPSI		Majority
	370 380 390 400	
244	VETMLVADQSMADFHGSG-LKHVLLTLFSVAARFYKHPSI	mADAMTS-1
12	VETLLVADASMAAFY GAD-LDNHLLTLM SVAARIYKHPSI	hADAMTS-2
147	VEVLVVAADNRMVSYHGEN-LQHYLLTLM SLD-----	hADAMTS-3
310	VELLLVADSSMAKMYGRG-LQHYLLTLASIANRLYSHASI	rADAMTS-4
220	VETLVVADDKMAAFHGAG-LKRYLLTVM AAAAKAFKHPSI	KIAA0688
254	IEVLLGVDDSVVRFHGKEHVQNYLLTLMNIVNEIYHDESL	KIAA0366
251	ADVLALADEAGYYFFNG----NYKVD----SPKNFNIAGT	KIAA0605
RNSISLVVVVKVVVLGDEKKGPEVSX-NAALT LRNF CNWQH		Majority
	410 420 430 440	
283	RNSISLVVVVKILVIYEEQKGPEVTS-NAALT LRNF CNWQK	mADAMTS-1
51	KNSINLMVVVKVLIVEDEKKGPEVSD-NGGLTL LRNF CNWQR	hADAMTS-2
177	-----GPSISF-NAQTTLKNLCQWQH	hADAMTS-3
349	ENHIRLAVVKVVVLTD--KSLEVSK-NAATT LKNFCKWQH	rADAMTS-4
259	RNPVSLVVT RLVILGSGEEGPQVGP-SAAQT LRSFCAWQR	KIAA0688
294	GVHINVV LVRMIMLG YAKSISLIERGNPSRSL ENVC RWAS	KIAA0366
283	VVKYR----RPM DVYETGIEYIVAQGPTNQGLNVM-VWNQ	KIAA0605
QHNSPSDRHPEHYDTAILLTRQDL CGSHG-CDTLGMADV G		Majority
	450 460 470 480	
322	QHNSPSDRDPEHYDTAILLTRQDL CGSHT-CDTLGMADV G	mADAMTS-1
90	RFNQPSDRHPEHYDTAILLTRQNF CGQEGLCDTLGVADIG	hADAMTS-2
197	SKNSPGGI---HHDTAVLLTRQDICRAHDKCDTLGLAELG	hADAMTS-3
386	QHNQLGDDHEEHYDAAILLTRREDL CGHHS-CDTLGMADV G	rADAMTS-4
298	GLNTPEDSDPDHFDTAILLTRQDL CGVST-CDTLGMADV G	KIAA0688
334	QQQRSDLNHSEHHDHAI FLTRQDF-GPAGM---QGYAPVT	KIAA0366
318	NGKSPSIT---FEYTL LQPPHE---SRPQPIYYGFSESA	KIAA0605

Fig. 17C

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TICDPXRSCSVIEDDGLQAAFTVAHELGHVFNMPHD - DSK													Majority																												
490			500			510			520																																
361	TVC	DPS	RSC	SVI	EDD	GLQ	AAFT	TAHEL	GHV	FN	M	PHD - DAK	mADAMTS-1																												
130	TIC	DPN	KSC	SVI	EDD	GLQ	AAHT	LAHEL	GHV	LS	M	PHD - DSK	hADAMTS-2																												
234	TIC	DPY	RSC	SI	EDS	GLS	TAF	TAHEL	GHV	FN	M	PHD - DNN	hADAMTS-3																												
425	TIC	SP	PER	SCA	VI	EDD	GLH	AAFT	VAHE	IGH	LL	GLSHD - DSK	rADAMTS-4																												
337	TVC	DPA	RSCA	IV	EDD	GLQ	SAFT	AAHEL	GHV	FN	M	LHD - NSK	KIAA0688																												
370	GMCH	PV	RSCT	LN	HED	GFSS	AFVVA	HET	GHV	L	G	MEHDGQGN	KIAA0366																												
351	-----ESQGLDGA-----GLMGFI PHNG----												KIAA0605																												
PC - SLNGPXGSSRHVM - APLLXHL DHSXPWSPCSAQEITE													Majority																												
530			540			550			560																																
400	HCAS	LNG	VT	GD	S	-HLM	-AS	MLSS	LDHS	QPW	SPCS	AYM	VTS	mADAMTS-1																											
169	PCTR	LE	FG	PM	GKH	-HVM	-AP	LFV	HLN	QTL	PWSP	CSAM	YLTE	hADAMTS-2																											
273	KCKE	-	-	EG	VKS	PQH	V	M	-A	PTLN	FYTNP	WMWS	KCSRKYITE	hADAMTS-3																											
464	FCE	EN	FGS	-	T	ED	KRL	M	-SS	IL	TSID	ASKP	WSKCTSATITE	rADAMTS-4																											
376	PCIS	LNG	PL	STS	RH	V	M	-AP	VMA	HVD	PEEP	WSPCS	ARFITD	KIAA0688																											
410	RC	-	-	-	G	DET	AMG	S	V	M	-AP	L	VQAA	FHRY	HWSRCS	GQEL	KR	KIAA0366																							
369	-	-	-	S	LYG	QASS	ERL	GLD	NRL	F	GHP	GLD	MEL	G	PS	Q	G	Q	E	T	N	E	KIAA0605																		
F - LDNGHGDCLLDKPEA - PLPLPVELPG - - ILYDADEQCO													Majority																												
570			580			590			600																																
438	F	-	L	D	N	G	H	G	E	C	L	M	D	K	P	Q	N	-	P	I	K	L	P	S	D	L	P	G	-	-	T	L	Y	D	A	N	R	Q	C	Q	mADAMTS-1
207	L	-	L	D	G	G	H	G	D	C	L	L	D	A	P	A	A	-	A	L	P	L	P	T	G	L	P	G	R	M	A	L	Y	Q	L	D	O	Q	C	R	hADAMTS-2
310	F	-	L	D	T	G	Y	G	E	C	L	L	N	E	P	E	S	R	P	Y	P	L	P	V	Q	L	P	G	-	-	I	L	Y	N	V	N	K	Q	C	E	hADAMTS-3
502	F	-	L	D	D	G	H	G	N	C	L	L	D	V	P	R	K	-	Q	I	L	G	P	E	E	L	P	G	Q	T	-	-	Y	D	A	T	Q	Q	C	N	rADAMTS-4
415	F	-	L	D	N	G	Y	G	H	C	L	L	D	K	P	E	A	-	P	L	H	L	P	V	T	F	P	G	K	D	-	-	Y	D	A	D	R	O	C	Q	KIAA0688
445	Y	-	I	H	S	Y	-	-	D	C	L	L	D	D	P	F	D	H	D	W	P	K	L	P	E	L	P	G	-	-	I	N	Y	S	M	D	E	Q	C	R	KIAA0366
406	V	C	E	Q	A	G	G	G	A	C	-	E	G	P	P	R	G	K	G	F	R	D	R	N	V	T	G	T	P	L	T	G	D	K	D	D	E	E	V	D	KIAA0605
LTFGPGSKHCPXFSA - DVCAQLWCAGVD - GGHXVCQTKHG													Majority																												
610			620			630			640																																
474	F	T	F	G	E	E	S	K	H	C	P	D	A	A	S	-	-	T	C	T	T	L	W	C	T	G	T	S	-	G	G	L	L	V	C	Q	T	K	H	-	mADAMTS-1
245	Q	I	F	G	P	D	F	R	H	C	P	N	T	S	A	Q	D	V	C	A	Q	L	W	C	H	-	T	D	-	G	A	E	P	L	C	H	T	K	N	G	hADAMTS-2
347	L	I	F	G	P	G	S	Q	V	C	P	Y	M	M	Q	-	-	-	C	R	R	L	W	C	N	N	V	N	-	G	V	H	K	G	C	R	T	Q	H	T	hADAMTS-3
538	L	T	F	G	P	E	Y	S	V	C	P	G	M	-	-	-	D	V	C	A	R	L	W	A	A	V	V	R	-	Q	G	Q	M	V	C	L	T	K	K	-	rADAMTS-4
451	L	T	F	G	P	D	S	R	H	C	P	Q	L	P	P	P	-	-	C	A	A	L	W	C	S	G	H	L	-	N	G	H	A	M	C	Q	T	K	H	S	KIAA0688
480	F	D	F	G	V	G	Y	K	M	C	T	A	F	R	T	F	D	P	C	K	Q	L	W	C	S	H	P	D	-	N	P	Y	-	F	C	K	T	K	K	G	KIAA0366
445	T	H	F	A	S	Q	-	-	-	E	F	F	S	A	N	A	I	S	D	Q	L	L	G	A	G	S	D	L	K	D	F	T	L	N	E	T	V	N	S	KIAA0605	

Fig. 17D

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- - PWADGTPCGPGKW - CKAGS - CVPKEENER - - PVVDGGW		Majority
	650 660 670 680	
510	- FFWADGTSCGEGKW - CVSGK - CVNKTDMKHFATPVHGSW	mADAMTS-1
283	SLPWADGTPCGPGHL - CSEGS - CLPEEEVERPKPVVDGGW	hADAMTS-2
383	- - PWADGTECEPGKH - CKYG - FCVPK - EMD - - VPVTDGSW	hADAMTS-3
573	- LPAVRALPVGKEESACKANVWTKLRKNITRHQAMEIGGP	rADAMTS-4
488	- - PWADGTPCGPAQA - CMGGR - CLHMDQLQDFNIPQAGGW	KIAA0688
518	- - PPLDGTCAAGKW - CYKGH - CMWKNANQQ - - - KQDGNW	KIAA0366
481	IFA - - QGAP - - - - RSSLAESFFVDYEENE - - - - -	KIAA0605
GPWGPWGDCSRTC GGGSVQFSLREC NNVPKNGGKYCEGR -		Majority
	690 700 710 720	
547	GPWGPWGDCSRTC GGGSVQYTMRECDNPVPKNGGKYCEGK -	mADAMTS-1
321	APWGPWGEC SRTC GGGSVQFSHRECKDPEPQNGGRYCLGR -	hADAMTS-2
416	GSWS PFGTCSRTC GGSGIKTAIRECNRPEPKNGGKYCVGR -	hADAMTS-3
612	GAPGV - - - - SVLALAGEEYSLPTAIAITPHLETVAATAQG	rADAMTS-4
524	GPWGPWGDCSRTC GGGSVQFSSRDCTRVPVPRNGGKYCEGR -	KIAA0688
551	GSWTKFGSCSRTC GTGVRFRTRQC NNMPINGGQDCPG - V	KIAA0366
504	- - - - - GAGPYLLNGSY - - LELSSDRVANSSS	KIAA0605
RAKYQSCNTEDCPKH XGKTFRAEQCAKYN - AFSYXNKGXX		Majority
	730 740 750 760	
586	RVR YRSCNIEDCPDNNGKTFREEQCEAHN - EFSKASFGNE	mADAMTS-1
360	RAKYQSCHTEECPPD - GKS FREQQCEKYN - AYN YTDMDGN	hADAMTS-2
455	RMKFKSCNTEPCLKOK - RDFRDEQCAHFDGKHFNIN - GLL	hADAMTS-3
648	RGPY - TVPAVSYP AHLTANLSATSSVKPKMAISPMOKESK	rADAMTS-4
563	RTRFRSCNTEDCPTGSALT FREEQCAAYN - HRTDLFKSFP	KIAA0688
590	NFEYQLCNTTEECQKHFE - DFRAQQCQRNSHFEYQNTKH -	KIAA0366
528	EAPFPNVSTSLLTSAGNRTHKARTRPKARKQ - - - - GVSPA	KIAA0605
PXVEWVPKYAGVSPKDRCKLTCRAKGTGYYYVLEPKVVVDG		Majority
	770 780 790 800	
625	PTVEWTPKYAGVSPKDRCKLTCEAKGIGYFFVLQPKVVVDG	mADAMTS-1
398	- LLQWVPKYAGVSPRDRCKLFCRARGRSEFKVFEAKVIDG	hADAMTS-2
493	PNVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDG	hADAMTS-3
687	TFVEWVPKYAGVLPADVCKLTCRAKGTGYVVVFSPKVTDG	rADAMTS-4
602	GPMDWVPRYTGVAPDQCKLTCQARALGYYYVLEPRVVVDG	KIAA0688
628	- - - HWLP - YEHPDPKKRCHLYCQSKETGDVAYMKQLVHDG	KIAA0366
564	DMYRWK - - - - - LSSHEPCSATCTTGVM SAY - - - - -	KIAA0605

Fig. 17E

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TPCS - PDSNSVCVRGQCVKAGCDEIIGSKKKFDKCGVCGG		Majority
	810 820 830 840	
665	TPCS - PDSTSVCVQGGQCVKAGCDRIIDS KKKFDKCGVCGG	mADAMTS-1
437	TLCG - PETLAICVRGQCVKAGCDHVVD SFWKLDKCGVCGG	hADAMTS-2
533	TPCG - QDTNDICVQGLCROAGCDHVLNSKARRDKCGVCGG	hADAMTS-3
727	TECR - PYSNSVCVRGRCVRTGCDGIIGSKLQYDKCGVCGG	rADAMTS-4
642	TPCS - PDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGG	KIAA0688
664	THCSYKDPYSICVRGECVKVGCDKEIGSNKVEDKCGVCGG	KIAA0366
589	-----AMCVR-----	KIAA0605
DGSSCKKVSGTFTKT--RYGYNDVVTIPAGATNILVRQRS		Majority
	850 860 870 880	
704	NGSTCKKMSGIVTST--RPGYHDIVTIPAGATNIEVKHRN	mADAMTS-1
476	KGNSCRKGSGLTPT--VYGYNDIVTIPAGATNIDVKQRS	hADAMTS-2
572	DNSSCKTVAGTFNT--HYGYNTVVRIPAGATNIDVRQHS	hADAMTS-3
766	DNSSCTKIIGTFNKK--SKGYTDVVRIPEGATHIKVRQFK	rADAMTS-4
681	DGSGCSKQSGSFRKF--RYGYNNVVTIPAGATHILVRQQG	KIAA0688
704	DNSHCRTVKGTFTTRTPRKLGYLKMFDIPPGARHVLIOEDE	KIAA0366
594	-----YDGV-----	KIAA0605
ASGHTN--NYLALKX-ADGEYLLNGNFTLSTSETDIDLKG		Majority
	890 900 910 920	
742	QRGSRNNGSFLAIRA-ADGTYILNGNFTLSTLEQDLTYKG	mADAMTS-1
514	HPGVQNDGNYLALKT-ADGQYLLNGNLAISAI EQDILVKG	hADAMTS-2
610	FSGETDDDNYLALSS-SKGEFLLNGNFVVTMAKREIRIGN	hADAMTS-3
804	AKDQTRFTAYLALKK-KTGEYLLNGKYMISTSETIIDING	rADAMTS-4
719	NPGHRS--IYLALKL-PDGSYALNGEYTLMPSP TDVVLPG	KIAA0688
744	ASPH-----ILA IKNQATGHYILNGKGEEAKSRTFIDL--	KIAA0366
598	-----	KIAA0605
TV-LRYSGSSAALERLHS----PLKEPLTVQVLAV-GXT-		Majority
	930 940 950 960	
781	TV-LRYSGSSAALERIRS--FSPLKEPLTIQVLMV-GHAL	mADAMTS-1
553	TI-LKYSGSIATLERLOS--FRPLPEPLTVQLLAVPGEVF	hADAMTS-2
649	AV-VEYSGSETAVERINST--RIEQELLLQVLSV-GKLY	hADAMTS-3
843	TV-MNYSYGWSHRDDFLHGMGYSATKEILIVQILA-TDPTK	rADAMTS-4
756	AVSLRYSGATAASETLSG--HGPLAQPLTLQVL-VAGNPQ	KIAA0688
777	GVEWDYN-IEDDIESLHTDG--PLHDPVIVLIIPQENDT-	KIAA0366
598	EVDDSYCDALTRPEPVHE-----	KIAA0605

Fig. 17F

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R P D V R Y S F F V P - - - - -		Majority
	970 980 990 1000	
817	R P K I K F T Y F M - - - - -	mADAMTS-1
590	P P K V K Y T F F V P N D - - - - -	hADAMTS-2
685	N P D V R Y S F N I P I E D K P - - - - - Q Q F Y W N S H G P W Q	hADAMTS-3
881	A L D V R H S F F V P - - - - -	rADAMTS-4
793	D T R L R Y S F F V P - - - - -	KIAA0688
813	R S S L T Y K Y I I H E D S V P T I N S N N V I Q E E L D T F E W - A L K S W S	KIAA0366
616	- - - - - F C A G R E C Q P R - - - - - W E T - S S W S	KIAA0605
- - - - -		Majority
	1010 1020 1030 1040	
827	- - - - -	mADAMTS-1
603	- - - - -	hADAMTS-2
713	A C S K P C Q G E R K - R K L V C T R E S D - - - Q L T V S D Q R C D R L P Q P	hADAMTS-3
892	- - - - -	rADAMTS-4
804	- - - - -	KIAA0688
852	Q V S K P C G G G F Q Y T K Y G C R R K S D - - - N K M V H R S F C E A N K K P	KIAA0366
633	E C S R T C G E G Y Q F R V V R C W K M L S P G F D S S V Y S D L C E A A E A V	KIAA0605
- - - - -		Majority
	1050 1060 1070 1080	
827	- - - - -	mADAMTS-1
603	- - - - - V - D F S - - -	hADAMTS-2
749	G H I - T E P C G T - D C D L R - W H V A S R S E C S A Q C G L - G Y R T L D I	hADAMTS-3
892	- - - - -	rADAMTS-4
804	- - - - -	KIAA0688
889	K P I - R R M C N I Q E C T H P L W V A E E W E H C T K T C G S S G Y Q L R T V	KIAA0366
673	R P E E R K T C R N P A C G - P Q W E M S E W S E C T A K C G E R S V V T R D I	KIAA0605
- - - - - K V T - - - S S N T R P T - R X X - - - - -		Majority
	1090 1100 1110 1120	
827	- - - - - K K K T E - - - S F N A I P T F - S E - - - - -	mADAMTS-1
607	- - - - - M Q S S K E R A T - - - T N I T Q P L L H A Q - - - - -	hADAMTS-2
785	Y C A K Y S R L D G K T E K V D D G F C S S H P K P S N R E K C S G E C N T G G	hADAMTS-3
892	- - - - -	rADAMTS-4
804	- - - - - R P T - - - P S T P R P T - P Q D - - - - -	KIAA0688
928	R C L Q - P L L D G T N R S V H S K Y C M G D - R P E S R R P C N R V P C P A Q	KIAA0366
712	R C S E - - - - - D E K L C D P N T R P V G E K N C T G P P C D R Q	KIAA0605

Fig. 17G

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		WV - GDWGECSKTCG - GTQRRXV - CRD - DG - V - - - SEC - KA				Majority
		1130	1140	1150	1160	
842	WVIEEWGECSKTCGSGWQRRVVQCRDINGHP - - ASECake					mADAMTS-1
627	WVLGDWSECSSTCGAGWQRRTECRDPSGQA - - SATCNKA					hADAMTS-2
825	WRYSAWTECSKSCDGGTQRRRAICVNTRNDVLDDSKCTHQ					hADAMTS-3
892	- - - - -					rADAMTS-4
817	WL - - - - - HRR A - - - - - Q I					KIAA0688
966	WKTGPWSECSVTCEGEGTEVRQVLCRAGDHCDEKPESVRA					KIAA0366
741	WTVSDWGPSCSGCGQGRITIRHVVYCKTSDGRVVPESQCOM -					KIAA0605
		- - LKPLXXRPC - - - KS - - CP - - W - - - DWS - - - - - C - -				Majority
		1170	1180	1190	1200	
880	- - VKPASTRPC - - - ADLPCP - HWQVGDWSP - - - - - CSK					mADAMTS-1
665	- - LKPEDAKPC - - - ES - - - - -					hADAMTS-2
865	- - EKVTIQR - C - - - SEFPCC - QWKS GDWSE - - - - - CLV					hADAMTS-3
892	- - - - -					rADAMTS-4
825	- - LEILRRRP - - - - - WA - - - - -					KIAA0688
1006	CQLPPCNDPECLGDKSIFCQ - MEVLARYCSIPGYNKLCCCE					KIAA0366
780	- ETKPLAIHPC - GDKN - - CPAHWLAQDWER - - - - - CNT					KIAA0605
		TCGK - - - - - KKPT -				Majority
		1210	1220	1230	1240	
907	TCGK - - - - - GYKKRTL					mADAMTS-1
676	- - - - -					hADAMTS-2
891	TCGK - - - - - GHKHRQV					hADAMTS-3
892	- - - - - KKPA X					rADAMTS-4
835	- - GR - - - - -					KIAA0688
1045	SCSKRSSTLPPPYLLEAAETHDDVISNPSDLPRSLVMPTS					KIAA0366
809	TCGRGVKKRLVLCMELANGKPQTRSGPECGLAK - - KPPEE					KIAA0605
		KV - - - - - SA - - - - - DT				Majority
		1250	1260	1270	1280	
918	KCV - - - - - SH - - - - - DG					mADAMTS-1
676	- - - - -					hADAMTS-2
902	WCQFGEDRLNDRMCDPEVDAAANSA - - - - - DT					hADAMTS-3
897	KVN - - - - - SA - - - - - DT					rADAMTS-4
837	- - - - -					KIAA0688
1085	LVPYHSETPAKKMSLSSISSVGGPNAYAAFRPNSK - - PDG					KIAA0366
847	STCF - - ERPCFKWYTSPWSECTKTCGVGVMRDVKCYQGT					KIAA0605

Fig. 17H

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	D G L - Q E S P - - P - - - - - P - - K P - - - - Q L C P L S Q C	Majority
	1290 1300 1310 1320	
925	G V L S N E S C - - D - - - - - P L K K P K H Y I D F C T L T Q C	mADAMTS-1
676	- - - - - Q L C P L	hADAMTS-2
929	D G L Q E S S P - - P - - - - - I P I W K P S I F S H V - P S S R I	hADAMTS-3
904	D G L - Q E S S - - P - - - - - P	rADAMTS-4
837	- - - - -	KIAA0688
1123	A N L R Q R S A - - Q Q A G S K T V R L V T V P S S P P T K R V H L S S A S Q M	KIAA0366
885	D I V R G C D P L V K P V G R Q A C D L Q P C P T E P P D D S C Q D Q P G T N C	KIAA0605
	A - - - - -	Majority
	1330 1340 1350 1360	
951	S	mADAMTS-1
681		hADAMTS-2
955	P	hADAMTS-3
912		rADAMTS-4
837	K	KIAA0688
1161	A A A S F F A A S D S I G A S S Q A R T S K K D G K I I D N R R P T R S S T L E	KIAA0366
925	A L A I - - - - - K V N L C G H W Y Y S K A C C R - - - S C R P P H S	KIAA0605
	-	Majority
951	-	mADAMTS-1
681		hADAMTS-2
955		hADAMTS-3
912		rADAMTS-4
837		KIAA0688
1201	R	KIAA0366
951		KIAA0605

Fig. 17I

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Bovine ADAMTS 4 DNA

TTTAGGGAGG AGCAGTGTGA GGCCAAAAT GGATATCAGT CTGATGCAAA AGGAGTCAAA	60
ACGTTTGTGG AATGGGTTC CAAATATGCT GGTGTCCTGC CCGGAGACGT GTGCAAACTG	120
ACCTGCAGAG CTAAGGGCAC TGGCTACTAC GTGGTGTCT CTCCAAAGGT GACCGATGGG	180
ACAGAGTGCA GGCCATACAG CAATTCCGTG TGTGTCCGGG GGAAGTGTGT GCGGACAGGC	240
TGTGACAGCA TCATTGGCTC GAAGCTGCAG TATGACAAAT GTGGCGTCTG TGGAGGAGAC	300
AACTCCAGTT GCACAAAGGT GGTCCGAACC TTCAATAAAA AAAGTAAGGG TTACACTGAC	360
GTCGTGAGGA TCCCCGAAGG GCGACTCAC ATAAAAGTCC GACAGTTCAA AGCCAAAGAC	420
CAG	423

Fig. 18

Bovine ADAMTS 4 Protein

FREEQCEAKNGYQSDAKGVKTFVEWVPKYAGVLPGDVCKLTCRAKGTGYVVVFSPKVTGTECRPYSNSVCVRGKCVRTG
CDSIIGSKLQYDKCGVCGGDNSSCTKVVGTFNKKSKGYTDVVRIPGATHIKVRQFKAKDQ

Fig. 19

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Bovine 0688 DNA

GGAAACCTG GCCATTGGA GCAACTACCT GGGCCTGAAG CTCCCCGATG GTCCTATGC	60
CCTCAACGGT GAATACACGC TGATCCCGTC CCCCACAGAC GTGGTACTGC CCGGGGCCGT	120
CAGCCTGCGC TACAGCGGGG CCACTGCAGC CTGGGAGACA CTGTCAGGAC ACGGGCCCT	180
GGCTGAGCCC TTAACGCTGC AGGTCTAGT GGCTGGCAAC CCGCAGAACG CCCGCCCTAG	240
ATACAGCTTT TTCGTGCCGC GACCGCGACC GGTCCTCTCC ACGCCACGCC CCACTCCCA	300
GGACTGGCTG CGCCGCAAGT CACAGATTCT GGAGATCCTC CGGCGGCGCT CCTGGGCCGG	360
CAGGAAATAA CCTCACCATC CCGGCTGCCC TTTCTGGGCA CCGGGGCTC GGACTTAGCT	420
GGGTGAACGA GAGACCTCTG CAGCGGCTC ACCCGAGAC ATCGTGGGG AGGGCTTAG	480
TGAGCCCCG CTCTCCTCCC CGCGTAACG AGCAGGCTGG CCCTGCCGGG GTTTCCTGCC	540
CTGGATGGCT GGTGGATGGA AGGGGCTGG AGATTGTCCC CTATCTAAAC TGCCCCCTCT	600
GCCCTGCTGG TCACAGGAGG GAGGGGAAG GCAGGGA	637

Fig. 20

Bovine KIAA 0688 Protein

ETLAIWSNYLALKLPDGSYALNGEYTLIPSPDVLPGAVSLRYSGATAASETLSGHGPLAEPLTLQVLVAGNPQNARLR
YSFFVPRPRPVPSTPRPTQDWLRRKSQILEILRRRSWAGRK

Fig. 21

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Human ADAMTS 5 DNA

```

ACTCACTATA GGGCTCGTGC GGCCGCCCGG GCAGGTATCT TTAAGCATCC CAGCATCCTC    60
AACCCCATCA ACATCGTTGT GGTC AAGGTG CTGCTTCTTA GAGATCGTGA CTCCGGGCCC    120
AAGGTCACCG GCAATGCGGC CCTGACGCTG CGCAACTTCT GTGCCTGGCA GAAGAAGCTG    180
AACAAAGTGA GTGACAAGCA CCCCAGTAC TGGGACACTG CCATCCTCTT CACCAGGCAG    240
GACCTGTGTG GAGCCACCAC CTGTGACACC CTGGGCATGG CTGATGTGGG TACCATGTGT    300
GACCCCAAGA GAAGTGCTC TGTATTGAG GACGATGGG TTCCATCAGC CTTCACTACT    360
GCCCACGAGC TGGGCCACGT GTTCAACATG CCCCATGACA ATGTGAAAGT CTGTGAGGAG    420
GTGTTTGGGA AGCTCCGAGC CAACCACATG ATGTCCCGA CCCTCATCCA GATCGACCGT    480
GCCAACCCCT GGTGAGCCTG CAGTGCTGCC ATCATCACCG ACTTTCTGGA CAGCGGGCAC    540
GGTGACTGCC TCCTGGACCA ACCCAGCAAG CCCATCTTCC TGCCGAGNGA TCTGCCGGGC    600
GCCAGCTACA CCCTGAGCCA GCARTGCGAG CTGGCTTTTG GCGTGGGCTT CAAGCCCTGT    660
CCTTACATGC AGTACTGCAC CAAGCTGTGG TGCAACGGGA AGGCCAAGGG ACAGATGGTG    720
TGCCAAACCC GCCACTTCCC CTGGGCCGAT GGCACCAAGT GTGGCGAGGG CAAGTTCTGC    780
CTCAAGGGGG CCTGCGTGGG AARACACAAC CTCACAAGC ACAGGGTGGA TGGTTCCTGG    840
GCCAAATGGG ATCCCTATGG CCCCTGCTCG CGCACATGTG GTGGGGGCGT GCAGCTGGCC    900
AGGAGGCAGN TGCACCAACC CCANCCCTG CCAACNGGGG GCAAGTACTG CGAGGGAGTG    960
AGGGTGAAT ACCGATCCTG CAACCTGGAG CCCTGCCCCA GCTCAGCCTC CGGAAAGAGC   1020
TTCCGGGAGG AGCAGTGTGA GGCTTTCAAC GGCTACAACC ACAGACCAA CCGGCTCACT   1080
CTCGCCGTGG CATGGGTGCC CAAGTACTCC GCGGTGCTC CCCGTGACAA GTGTAAGCTC   1140
ATC                                                                    1143

```

Fig. 22

Human ADAMTS 5 Protein

```

THYRARAARAGIFKHPSILNPINIVVVKVLLLRDRDSGPKVTGNAALTLRNFCAWQKLNKVS DKHPEYWDTAILFTRQ
DLCGATTCDTLGMADVGTMDPKRSCSVIEDDLPSAFTTAHELGHVFNMPHDNVKVCEEVFGKLRANHMMSP TLIQIDR
ANPWSACSAAIITDFLDSGHGDCLLDQPSKPIFLPXDLPGASYTLSQCELAFGVGFKPCPYMQYCTKLWCTGKAKGMV
CQTRHFPWADGTSCGEGFKLKGACVEXHNLNKHVRVDSWAKNDPYGPCSRTCGGGVQLARRQXHQXP LPTGGKYCEGV
RVKYRSCNLEPCSSASGKSFREEQCEAFNGYNHSTNRLTLAVAWPKYSGVSPRDKCKLI

```

Fig. 23

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Rat ADAMTS 2 DNA

TCCGCCCTTC CGGGAGGAAC AGTGTGAAAA ATATAATGCC TACAACCACA CGGACCTGGA	60
TGGGAATTTC CTTCAAGTGGG TCCCCAAATA CTCAGGAGTG TCCCCCGAG ACCGATGCAA	120
ACTGTTTTGC AGAGCCCGTG GGAGGAGTGA GTTCAAAGTG TTTGAACTA AGGTGATCGA	180
TGGCACTCTG TGGGACCGG ATACTCTGGC CATCTGTGTG CGGGGACAGT GCGTTAAGGC	240
TGGCTGTGAC CATGTGGTGA ACTCACCTAA GAAGCTGGAC AAGTGGGTA TCTGTGG	297

Fig. 24

Rat ADAMTS 2 Protein

PPFREEQCEKYNAYNHTDLGNFLQWVPKYSVSPDRCKLFCRARGRSEFKVFETKVIDGTLGGPDTLAICVRGQCVKA
GCDHVVNSPKKLDKCGIC

Fig. 25

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Rat ADAMTS 3 DNA

CCCCTGGATG TGGTCAAAGT GCAGTCGGAA GTACATCACC GAGTTCCTAG ACACTGGGTA	60
TGGAGAGTGC TTGTAAATG AACCTCAATC CAGSACCTAT CCTTTGCCTT CCCAACTGCC	120
CGGCCTTCTC TACAACGTGA ATAAACAATG TGAAGTATT TTTGGACCAG GCTCTCAAGT	180
GTGCCCATAT ATGATGCACT GCAGACGGCT CTGGTGCAAT AACGTGGATG GAGCACACAA	240
AGGCTGCAGG ACTCAGCACA CGCCCTGGGC AGATGGAACC GAGTGTGAGC CTGGAAGCA	300
CTGCAAGTTT GGATTCTGTG TTCCCAAAGA AATGGAGGGC CCTGCAATTG ATGGATCCTG	360
GGGAAGTTGG AGTCACTTTG GGGCCTGCTC AAGAACATGT GGAGGAGGCA TCAGAACAGC	420
CATCAGAGAG TGCAACAGAC CAGAGCCAAA AAATGGTGGG AGGTACTGTG TAGGGAGGAG	480
AATRAAGTTC AAATCCTGCA ACACCGAGCC CTGCCCCAAG CACAAGCGAG ACTTCCGTGA	540
GGAGCAGTGT GCTTACTTTG ACGGCAAGCA TTTCAACATC AATGGTCTGC TGCCCAAGTGT	600
ACGCTGGGTC CCTAAGTACA GTGGAATTTT GATGAAGGAC CGATGCAAGT TGTTCGACG	660
AGTGGCAGGA AACACAGCCT ACTACCAGCT TCGAGACAGA GTGATTGACG GAACCCCTG	720
TGGCCAGGAC ACAAATGACA TCTGTGTCCA AGGCCTTTGC CGGCAAGCTG GATGTGATCA	780
TACTTTAAAC TCAAAGGCCG GAAAGATAA ATGTGGGATT TGT	823

Fig. 26

Rat ADAMTS 3 Protein

PWMWSKCSRKYITEFLDTGYGECLLNEPQSRTYPLPSQLPGLLYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVDGAHK
 GCRTQHTPWADGTECEPGKHCKFGFCVPKEMEGPAIDGSWGSWSHFGACSRTCGGGIRTAIRECNRPEPKNGGRYCVGRR
 XKFKSCNTEPCPKHKRDFREEQCAYFDGKHFNINGLLPSVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPC
 GQDNDICVQGLCRQAGCDHTLNSKARKDKCGIC

Fig. 27

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brevican + TS-4

brevican

Fig. 28

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MOFVSMATLLTLLVRDLAEMGSPDAAAARVKKDRLHPRQVKLLETGLGEYEVSPIRVNALGEFPPTNVHFKRTRRSINSAT
 DPWPAFASSSSSTSSQAHYRLSAFGQQLFNL TANAGFIAPLFTVTLTGTPGVNQTKFYSEEEAELKHCFYKGYVNTNS
 EHTAVISLCSGMLGTFRSHDGYFIEPLQSMDEQEDEEQNKPHIYRRSAPQREPSTGRHACDTSEHKNRHSKDKKTR
 ARKWGERINLAGDVAALNSGLATEAF SAYGNKTDNTREKQTHRTKRFLSYPRFVEVLVWADNRWVS YHGENLQHYILTL
 MSIVASYKDPISIGNL INIVIVNLIVIHNEQDGPSISFNAQTLLKNL CQWQHSKNSPGGIHHD TAVLLTRQDICRAHDKC
 DTLGLAELGTICDPYRSCSISEDGSLSTAFTHAELGHVFNPHDDNNKCKEEGVKSPQHVMAPTLLNFYTNPMWMSKCSR
 KYTFEFLDTGYGECLLNEPESRPVLPVQLPGILYNVKNQCELIFGPGSQVCPYMQCRRLWCNNVNGVHKGCRTQHTPIW
 ADGTECEPKHKYGFVCPKEMDVPVTDGSGSWSPFGTCSRTCGGGIKTAIRECNRPKNGGKYCVGRMRMKFSCNTE
 PCLKQKRDFRDEQCAHFDGKHFNINGLLPNVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGGQTDNDICV
 QGLCRQAGCDHVLNSKARRDKCGVCGDSSCKTVAGTFNTVHYGNTVWRIPAGATNIDVRQHSFSGETDDDNVYALSS
 SKGEFLNGNFWVTMAKREIRIGNAVVEYSGETAVERINSTDRIEQELLQVLSVGKLYNPDPVRYSFNIPIEDKPPQFY
 WNSHGPNQACSKPCQGERKRLVCTRESQQLTVSDQRCRLPOPGHITTEPCGTDCDLRWHVASRSECSAQCGLGYRTLDI
 YCAKYSRLDGKTEKVDGFGCSSHPKPSNREKCSGECNTGGWRYSAWTECSKCDGGTQRRRAICVNTRNDVLDSDSKCTHQ
 EKVTIQRCEFPQPMKSGDWSEVRWEGCYFP

cysteine switch *
 potential furin cleavage sites → metalloprotease domain
 Zn binding
 Met turn
 disintegrin-like domain
 TSP 1 motif
 spacer region
 TSP1-like submotif 1
 TSP1-like submotif 2
 TSP1-like submotif 3

Fig. 29

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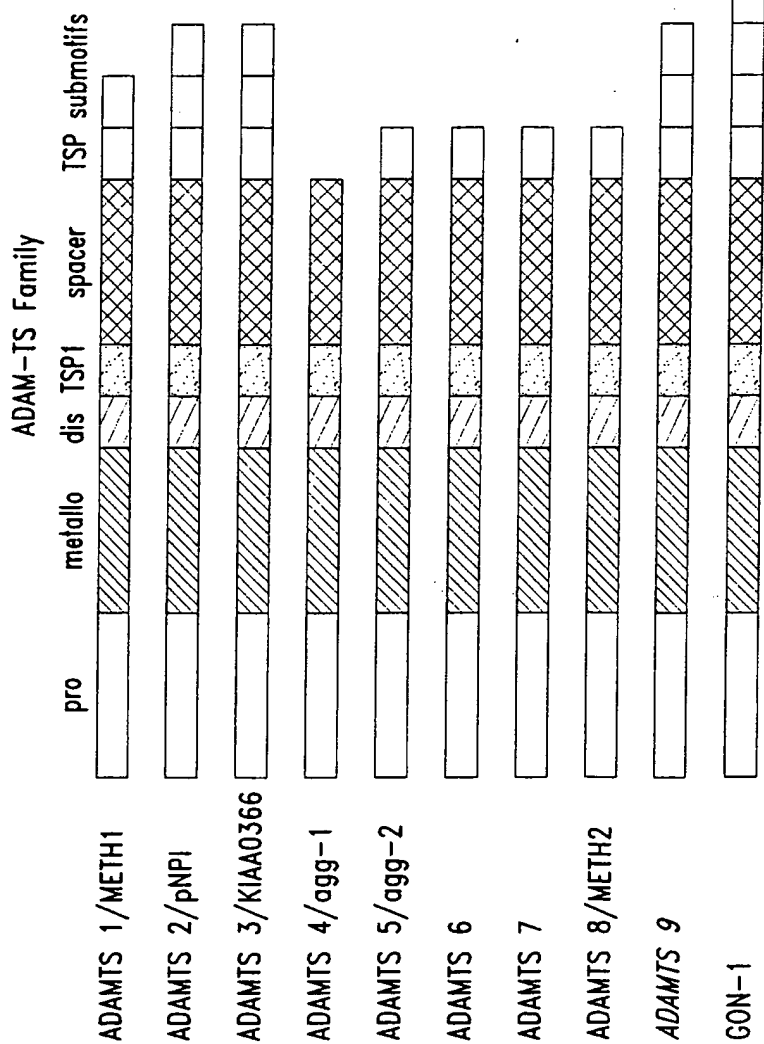


Fig. 30A

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CONSENSUS	HEXXHXXGXXHD
Fertilin α	HELGHNLGIRHD
ADAM 17/TACE	HELGHNFGAEHD
ADAM 10/Kuz	HEIGHNFGSPHD
ADAMTS 1	HELGHVFNMPHD
ADAMTS 2	HETGHVLGMEHD
ADAMTS 4	HELGHVFNMLHD
ADAMTS 5	HEIGHLLGLSHD
ADAMTS 9	HELGHVFNMPHD
GON-1	HELGHVFSIPHD

Fig. 30B

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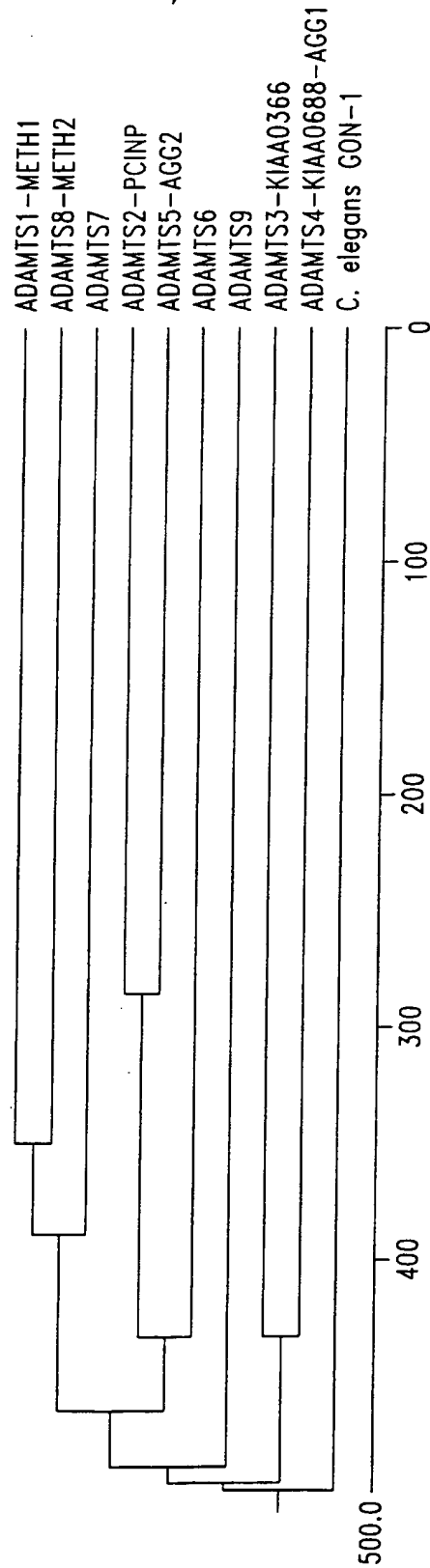


Fig. 30C

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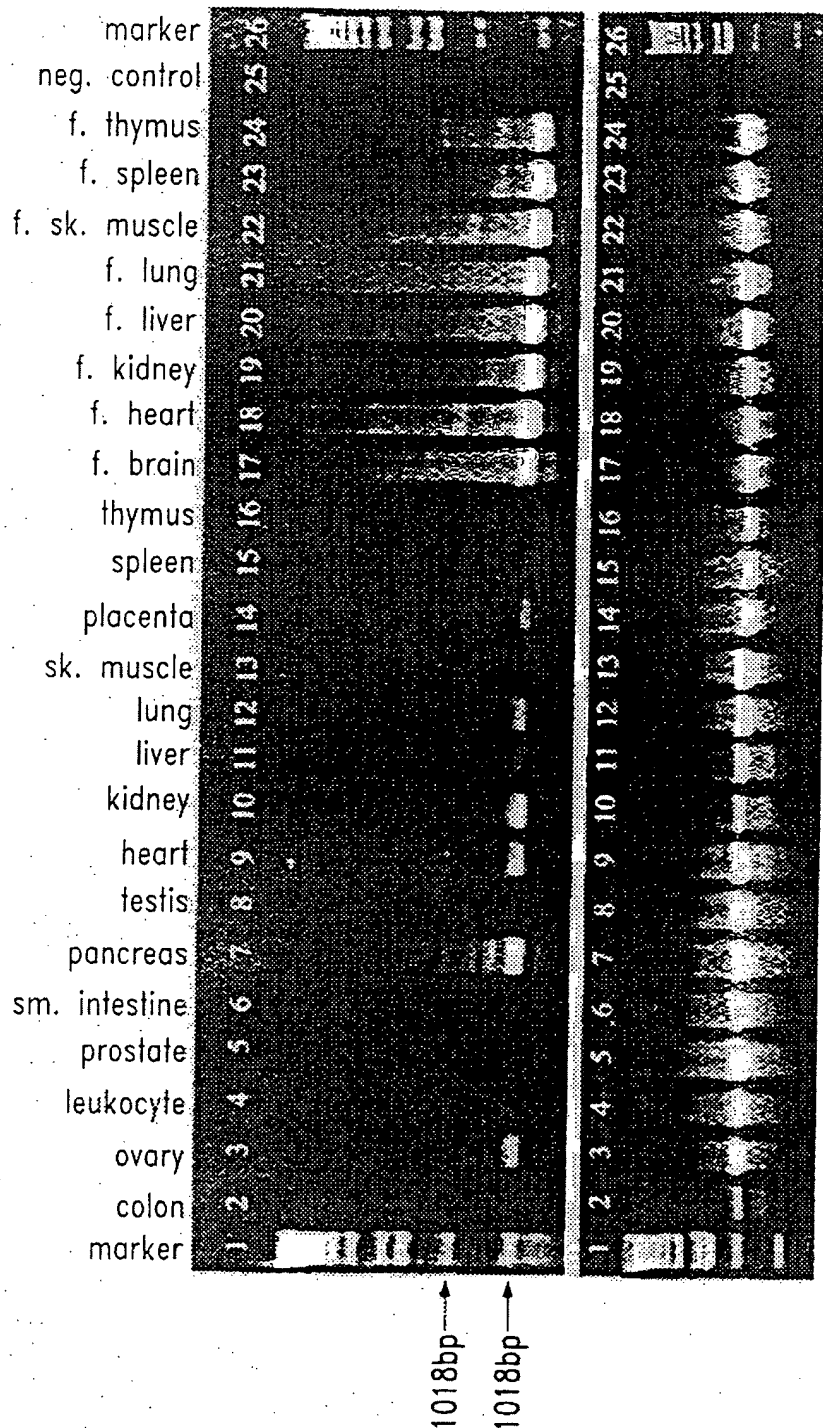


Fig. 31

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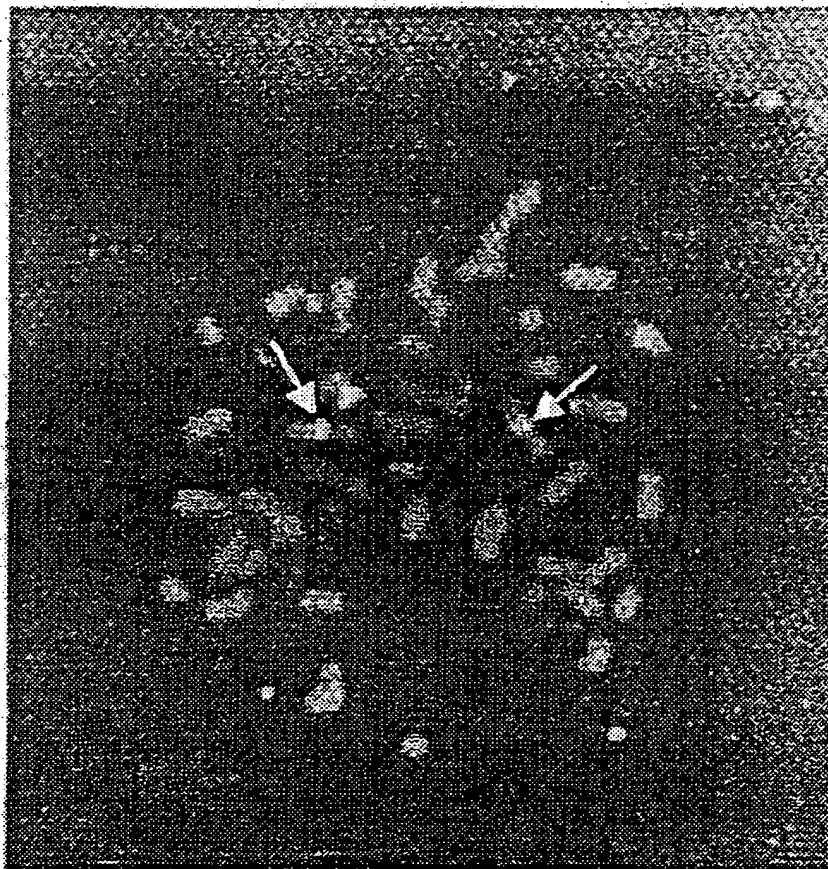


Fig. 32A

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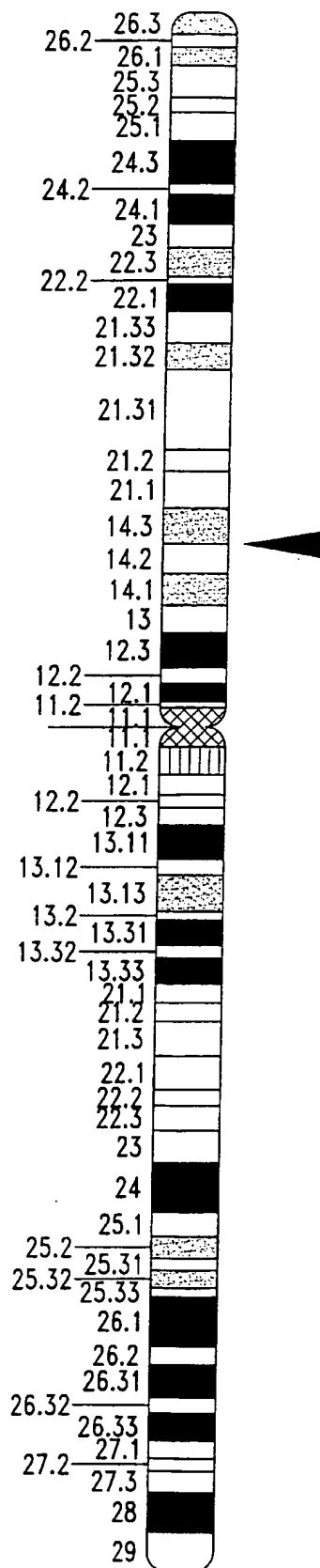
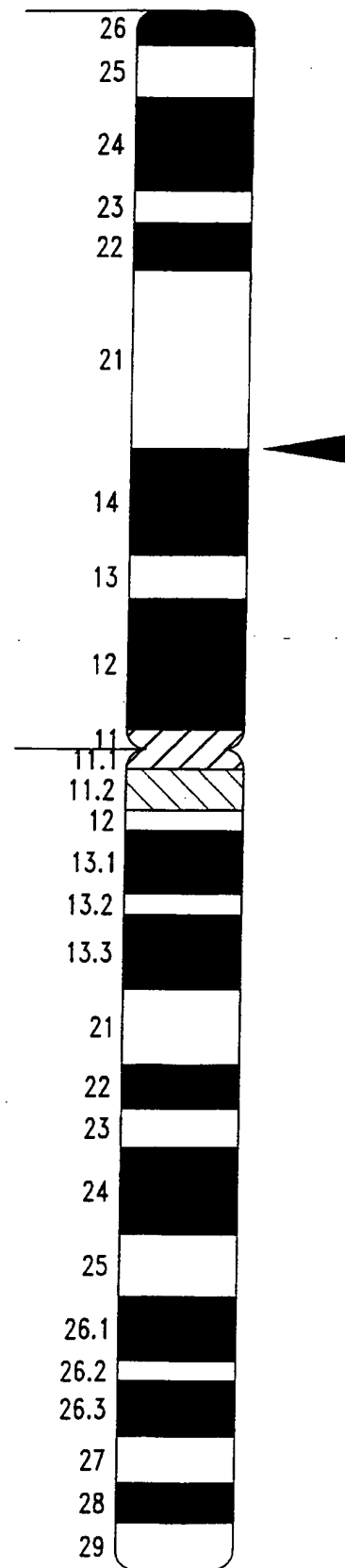


Fig. 32B

SEQUENCE LISTING

<110> Neurocrine Biosciences, Inc.
Kelner, Gregory S.
Clark, Melody
Maki, Richard A.

<120> METALLOPROTEINASES AND METHODS OF USE
THEREFOR

<130> 690068.453PC

<140> PCT

<141> 2000-03-08

<160> 51

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 2346

<212> DNA

<213> Homo sapien

<400> 1

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gcagcccgaa	tctacaagca	ccccagcatc	aagaattcca	tcaacctgat	ggtggtaaaa	180
gtgctgatcg	tagaagatga	aaaaatggggc	ccagagggtgt	ccgacaatgg	ggggcttaca	240
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cagcagtgca	ggcagatctt	tgggcccgat	ttccgccact	gccccaacac	ctctgctcag	780
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ccagctgggtg	ccactaatat	tgacgtgaag	cagcggagcc	acccgggtgt	gcagaacgat	1560
gggaactacc	tggcgctgaa	gacggctgat	gggcagtagc	tgctcaacgg	caacctggcc	1620
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<211> 680

<212> PRT

<213> Homo sapien

<400> 2

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His Ile Leu Thr Leu Met Ser Val Ala Ala Arg Ile Tyr Lys His Pro
35     40     45
Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu Ile Val
50     55     60
Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly Leu Thr
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Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro Ser Asp
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Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg Gln Asn
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Phe Cys Gly Gln Glu Gly Leu Cys Asp Thr Leu Gly Val Ala Asp Ile
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Gly Thr Ile Cys Asp Pro Asn Lys Ser Cys Ser Val Ile Glu Asp Glu
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Gly Leu Gln Ala Ala His Thr Leu Ala His Glu Leu Gly His Val Leu
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Ser Met Pro His Asp Asp Ser Lys Pro Cys Thr Arg Leu Phe Gly Pro
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Met Gly Lys His His Val Met Ala Pro Leu Phe Val His Leu Asn Gln
180    185    190
Thr Leu Pro Trp Ser Pro Cys Ser Ala Met Tyr Leu Thr Glu Leu Leu
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Asp Gly Gly His Gly Asp Cys Leu Leu Asp Ala Pro Ala Ala Ala Leu
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Pro Leu Pro Thr Gly Leu Pro Gly Arg Met Ala Leu Tyr Gln Leu Asp
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Gln Gln Cys Arg Gln Ile Phe Gly Pro Asp Phe Arg His Cys Pro Asn
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Ala Glu Pro Leu Cys His Thr Lys Asn Gly Ser Leu Pro Trp Ala Asp
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 Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln Cys Glu
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 Lys Tyr Asn Ala Tyr Asn Tyr Thr Asp Met Asp Gly Asn Leu Leu Gln
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 Trp Val Pro Lys Tyr Ala Gly Val Ser Pro Arg Asp Arg Cys Lys Leu
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 420 425 430
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 465 470 475 480
 Arg Lys Gly Ser Gly Ser Leu Thr Pro Thr Asn Tyr Gly Tyr Asn Asp
 485 490 495
 Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Lys Gln Arg
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 Val Lys Tyr Thr Phe Phe Val Pro Asn Asp Val Asp Phe Ser Met Gln
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 Ser Ser Lys Glu Arg Ala Thr Thr Asn Ile Thr Gln Pro Leu Leu His
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<211> 2751

<212> DNA

<213> Rattus norvegicus

<400> 3

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<211> 870

<212> PRT

<213> Rattus norvegicus

<220>

<221> VARIANT

<222> (1)...(870)

<223> Xaa = Any Amino Acid

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Gln Asp Lys Thr Arg Gln Pro Arg Ala Ala Ala Ala Ala Ala Gln Pro
 35           40           45
Asp Gln Arg Gln Trp Glu Glu Thr Gln Glu Arg Gly His Leu Gln Pro
 50           55           60
Leu Ala Arg Gln Arg Arg Ser Ser Gly Leu Val Gln Asn Ile Asp Gln
 65           70           75           80
Leu Tyr Ser Gly Gly Gly Lys Val Gly Tyr Leu Val Tyr Ala Gly Gly
 85           90           95
Arg Arg Phe Leu Leu Asp Leu Glu Arg Asp Asp Thr Val Gly Ala Ala
 100          105          110
Gly Gly Ile Val Thr Ala Gly Gly Leu Ser Ala Ser Ser Gly His Arg
 115          120          125
Gly His Cys Phe Tyr Arg Gly Thr Val Asp Gly Ser Pro Arg Ser Leu
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His Ala Arg Tyr Thr Leu Arg Pro Leu Leu Arg Gly Ser Trp Ala Glu
 165          170          175
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Thr Arg Glu Gly Phe Ser Phe Glu Ala Leu Pro Pro Arg Thr Ser Cys
 195          200          205
Glu Thr Pro Ala Ser Pro Ser Gly Ala Gln Glu Ser Pro Ser Val His
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Arg Arg Arg Arg Ser Ile Ser Arg Ala Arg Gln Val Glu Leu Leu Leu
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Tyr Leu Leu Thr Leu Ala Ser Ile Ala Asn Arg Leu Tyr Ser His Ala
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Thr Asp Lys Ser Leu Glu Val Ser Lys Asn Ala Ala Thr Thr Leu Lys
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Asn Phe Cys Lys Trp Gln His Gln His Asn Gln Leu Gly Asp Asp His
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Glu Glu His Tyr Asp Ala Ala Ile Leu Phe Thr Arg Glu Asp Leu Cys
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Gly His His Ser Cys Asp Thr Leu Gly Met Ala Asp Val Gly Thr Ile
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Cys Ser Pro Glu Arg Ser Cys Ala Val Ile Glu Asp Asp Gly Leu His
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 His Gly Asn Cys Leu Leu Asp Val Pro Arg Lys Gln Ile Leu Gly Pro
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 Thr Phe Gly Pro Glu Tyr Ser Val Cys Pro Gly Met Asp Val Cys Ala
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 515 520 525
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 660 665 670
 Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
 675 680 685
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 690 695 700
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 705 710 715 720
 Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Ile Ile Gly Thr Phe Asn
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 Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
 740 745 750
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 770 775 780
 Gly Lys Tyr Met Ile Ser Thr Ser Glu Thr Ile Ile Asp Ile Asn Gly
 785 790 795 800
 Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg Asp Asp Phe Leu His
 805 810 815
 Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu Ile Val Gln Ile Leu
 820 825 830
 Ala Thr Asp Pro Thr Lys Ala Leu Asp Val Arg Tyr Ser Phe Phe Val

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 Leu Val Leu Glu Arg Pro
 865 870

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 <213> Homo sapien

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<211> 951

<212> PRT

<213> Homo sapien

<400> 6

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Gly Gly Val Thr Ser Gln Glu Arg His Cys Leu Gln Gln Arg Arg Lys
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Ser Val Pro Gly Pro Gly Asn Arg Thr Cys Thr Gly Thr Ser Lys Arg
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Tyr Gln Leu Cys Arg Val Gln Glu Cys Pro Pro Asp Gly Arg Ser Phe
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Arg Glu Glu Gln Cys Val Ser Phe Asn Ser His Val Tyr Asn Gly Arg
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Ser Lys Pro Cys Asp Leu His Cys Thr Thr Val Asp Gly Gln Arg Gln
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Arg Gly Val Cys Val Ser Gly Lys Cys Glu Pro Ile Gly Cys Asp Gly

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<210> 10

<211> 958

<212> PRT

<213> Homo sapien

<400> 10

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20          25          30
Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp Glu Gln Glu Asp
35          40          45
Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro
50          55          60
Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His
65          70          75          80
Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
85          90          95
Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala Leu Asn Ser Gly
100         105         110
Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys Thr Asp Asn Thr
115         120         125
Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe Leu Ser Tyr Pro
130         135         140

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Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg Met Val Ser Tyr
 145 150 155 160
 His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile Asp
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 Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Leu Cys
 180 185 190
 Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr
 195 200 205
 Ala Val Leu Leu Thr Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys
 210 215 220
 Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg
 225 230 235 240
 Ser Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile
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 Ala His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn
 260 265 270
 Lys Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro
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 Thr Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg
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 Lys Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu
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 Asn Glu Pro Glu Ser Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly
 325 330 335
 Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly
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 Ser Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Cys Asn
 355 360 365
 Asn Val Asn Gly Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp
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 Ala Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Tyr Gly Phe
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 Cys Val Pro Lys Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly
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 Ser Trp Ser Pro Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile
 420 425 430
 Lys Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly
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 Lys Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu
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 Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His
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 Phe Asp Gly Lys His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg
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 Trp Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu
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 530 535 540
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
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 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
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 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr

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Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
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Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
      625      630      635      640
Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
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Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
      660      665      670
Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
      675      680      685
Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
      690      695      700
Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
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Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
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Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
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Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
      755      760      765
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Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
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Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
      805      810      815
Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
      820      825      830
Cys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile Cys
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Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His Gln
      850      855      860
Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln Trp
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Lys Ser Gly Asp Trp Ser Glu Cys Leu Val Thr Cys Gly Lys Gly His
      885      890      895
Lys His Arg Gln Val Trp Cys Gln Phe Gly Glu Asp Arg Leu Asn Asp
      900      905      910
Arg Met Cys Asp Pro Glu Val Asp Ala Ala Ala Asn Ser Ala Asp Thr
      915      920      925
Asp Gly Leu Gln Glu Ser Ser Pro Pro Ile Pro Ile Trp Lys Pro Ser
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Ile Phe Ser His Val Pro Ser Ser Arg Ile Pro Phe Ile Gly
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<210> 11

<211> 4303

<212> DNA

<213> Homo sapien

<400> 11

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<210> 12

<211> 840

<212> PRT

<213> Homo sapien

<400> 12

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Trp Leu Val Trp Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
35          40          45
Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
50          55          60
Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Thr Pro Ala Arg
65          70          75          80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
85          90          95
Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu
100          105          110
Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
115          120          125
Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
130          135          140
Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
145          150          155          160
His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
165          170          175
Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
180          185          190
Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
195          200          205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
210          215          220
Val Ala Asp Asp Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg
225          230          235          240
Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
245          250          255

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 Ser Asp Pro Asp His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp
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 Leu Cys Gly Val Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly
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 Thr Val Cys Asp Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly
 340 345 350
 Leu Gln Ser Ala Phe Thr Ala Ala His Glu Leu Gly His Val Phe Asn
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 Met Leu His Asp Asn Ser Lys Pro Cys Ile Ser Leu Asn Gly Pro Leu
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 Ser Thr Ser Arg His Val Met Ala Pro Val Met Ala His Val Asp Pro
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 Glu Glu Pro Trp Ser Pro Cys Ser Ala Arg Phe Ile Thr Asp Phe Leu
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 Asp Asn Gly Tyr Gly His Cys Leu Leu Asp Lys Pro Glu Ala Pro Leu
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 Pro Pro Cys Ala Ala Leu Trp Cys Ser Gly His Leu Asn Gly His Ala
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 Met Cys Gln Thr Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly
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 Pro Ala Gln Ala Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu
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 Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
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 Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr

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Ile Pro Ala Gly Ala Thr His Ile Leu Val Arg Gln Gln Gly Asn Pro		
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Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr		720
	725	730
Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val		735
	740	745
Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser		750
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Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln		765
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Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe		780
785	790	795
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp		800
	805	810
Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro		815
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Trp Ala Gly Arg Lys Phe Ile Gly		830
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 <211> 1518
 <212> DNA
 <213> Rattus norvegicus

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aagtcttgcc tcaaggagc ctgctggag agacacaacc caaacaagta ccgggtggac	1320
ggcccttggg ccaagtggga gccttatggt ccctgctcgc gcacctgcgg tggggcgcg	1380
cagctggccc ggaggcaagt gcaagcaacc ctaccctgc caacgggcgg gaagtactgc	1440
gagggagtga gagtgaata ccgatcttgc aacttggagc cctgccccag ctcagcctct	1500
ggcaagagct tccgggaa	1518

<210> 14

<211> 505

<212> PRT

<213> Rattus norvegicus

<400> 14

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Thr His Tyr Arg Ala Arg Ala Ala Arg Ala Gly Gln Arg Leu Thr
 1          5          10          15
Gly Ser Ser Leu Asp Leu Arg Arg Cys Phe Tyr Ser Gly Tyr Val Asn
      20          25          30
Ala Glu Pro Asp Ser Phe Ala Ala Val Ser Leu Cys Gly Gly Leu Arg
      35          40          45
Gly Ala Phe Gly Tyr Gln Gly Ala Glu Tyr Val Ile Ser Pro Leu Pro
      50          55          60
Asn Thr Ser Ala Pro Glu Ala Gln Arg His Ser Gln Gly Ala His Leu
      65          70          75          80
Leu Gln Arg Arg Gly Ala Pro Val Gly Pro Ser Gly Asp Pro Thr Ser
      85          90          95
Arg Cys Gly Val Ala Ser Gly Trp Asn Pro Ala Ile Leu Arg Ala Leu
      100          105          110
Asp Pro Tyr Lys Pro Arg Arg Thr Gly Val Gly Glu Ser His Asn Arg
      115          120          125
Arg Arg Ser Gly Arg Ala Lys Arg Phe Val Ser Ile Pro Arg Tyr Val
      130          135          140
Glu Thr Leu Val Val Ala Asp Glu Ser Met Val Lys Phe His Gly Ala
      145          150          155          160
Asp Leu Glu His Tyr Leu Leu Thr Leu Leu Ala Thr Ala Ala Arg Leu
      165          170          175
Tyr Arg His Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys
      180          185          190
Val Leu Leu Leu Gly Asp Arg Asp Thr Gly Pro Lys Val Thr Gly Asn
      195          200          205
Ala Ala Leu Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn
      210          215          220
Lys Val Ser Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe
      225          230          235          240
Thr Arg Gln Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met
      245          250          255
Ala Asp Val Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile
      260          265          270
Glu Asp Asp Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly
      275          280          285
His Val Phe Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val
      290          295          300
Phe Gly Lys Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln
      305          310          315          320
Ile Asp Arg Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr
      325          330          335
Asp Phe Leu Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser
      340          345          350
Lys Pro Ile Thr Leu Pro Glu Asp Leu Pro Gly Thr Ser Tyr Ser Leu
      355          360          365
Ser Gln Gln Cys Glu Leu Ala Phe Gly Val Gly Ser Lys Pro Cys Pro
      370          375          380
Tyr Met Gln Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly
      385          390          395          400

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Gln Met Val Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser
 405 410 415
 Cys Gly Glu Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Arg His
 420 425 430
 Asn Pro Asn Lys Tyr Arg Val Asp Gly Pro Trp Ala Lys Trp Glu Pro
 435 440 445
 Tyr Gly Pro Cys Ser Arg Thr Cys Gly Gly Gly Ala Gln Leu Ala Arg
 450 455 460
 Arg Gln Val Gln Ala Thr Leu Pro Leu Pro Thr Gly Gly Lys Tyr Cys
 465 470 475 480
 Glu Gly Val Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro
 485 490 495
 Ser Ser Ala Ser Gly Lys Ser Phe Arg
 500 505

<210> 15
 <211> 1455
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(1455)
 <223> n = A,T,C or G

<400> 15
 gatgcatcta agccctgggc caaatgcact tcagccacca tcacagaatt cctggatgat 60
 ggccatggta actgtttgct ggacctacca cgaaagcaga tcctgggccc cgaagaactc 120
 ccaggacaga cctacgatgc caccagcag tgcaacctta cattcggggc tgagtactcc 180
 gtgtgtcccc gcatggatgt ctgtgtctcc ctgtgtgtgt ctgtggtacg ccagggccag 240
 atggtctgtc tgaccaagaa gcttctgtcg gtggaaggga cgccttgtgg aaaggggaga 300
 atctgcctgc agggcaaatg tgtggacaaa accaagaaaa aatattattc aacgtcaagc 360
 catggcaact ggggatcttg gggatcctgg ggccagtgtt ctgcctcatg tggaggagga 420
 gtgcagtttg cctatcgctg ctgtaataac cctgtctcca gaaacaacgg acgctactgc 480
 acagggaaga gggccatcta ccgctcctgc agtctcatgc cctgcccacc caatggtaaa 540
 tcatttcgtc atgaacagtg tgaggccaaa aatggctatc agtctgatgc aaaaggagtc 600
 aaaacttttg tggaaatggg tcccaaatat gcaagtgtcc tgcccagcga tgtgtgcaag 660
 ctgacctgca gagccaaagg gactggctac tatgtggtat tttctccaaa ggtgaccgat 720
 ggcactgaat gtaggccgta cagtaattcc gtctgcgtcc gggggaagtg tgtgagaact 780
 ggctgtgacg gcatcattgg ctcaaagctg cagtatgaca agtgccgagt atgtggagga 840
 gacaactcca gctgtacaaa gattgttggg acctttaata agaaaagtaa gggttcanct 900
 gacgtggtga ggattcctga aggggcaacc cacataaaag ttcgacagtt caaagccaaa 960
 gaccagacta gattcactgc ctatttagcc ctgaaaaaga aaaacggtga gtaccttatc 1020
 aatggaaagt acatgatctc cacttcagag actatcattg acatcaatgg aacagtcatt 1080
 aactatagcg gttggagcca cagggatgac ttctgtcatg gcatgggcta ctctgccacg 1140
 aaggaaattc taatagtgca gattcttgca acagacccca ctaaaccatt agatgtccgt 1200
 tatagctttt ttgttcccaa gaagtcact ccaaaagtaa actctgtcac tagtcatggc 1260
 agcaataaag tgggatacaca cacttcgcag ccgcagtggg tcacggggcc atggctcgcc 1320
 tgctctagga cctgtgacac aggttggcac accagaacgg tgcaagtcca ggatggaaac 1380
 cggaagttag caaaaggatg tcctctctcc caaaggcctt ctgcgtttta gcaatgcttg 1440
 ttgaagaat gttag 1455

<210> 16
 <211> 484

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(484)

<223> Xaa = Any Amino Acid

<400> 16

Asp Ala Ser Lys Pro Trp Ser Lys Cys Thr Ser Ala Thr Ile Thr Glu
 1 5 10 15
 Phe Leu Asp Asp Gly His Gly Asn Cys Leu Leu Asp Leu Pro Arg Lys
 20 25 30
 Gln Ile Leu Gly Pro Glu Glu Leu Pro Gly Gln Thr Tyr Asp Ala Thr
 35 40 45
 Gln Gln Cys Asn Leu Thr Phe Gly Pro Glu Tyr Ser Val Cys Pro Gly
 50 55 60
 Met Asp Val Cys Ala Pro Leu Trp Cys Ala Val Val Arg Gln Gly Gln
 65 70 75 80
 Met Val Cys Leu Thr Lys Lys Leu Pro Ala Val Glu Gly Thr Pro Cys
 85 90 95
 Gly Lys Gly Arg Ile Cys Leu Gln Gly Lys Cys Val Asp Lys Thr Lys
 100 105 110
 Lys Lys Tyr Tyr Ser Thr Ser Ser His Gly Asn Trp Gly Ser Trp Gly
 115 120 125
 Ser Trp Gly Gln Cys Ser Arg Ser Cys Gly Gly Gly Val Gln Phe Ala
 130 135 140
 Tyr Arg Arg Cys Asn Asn Pro Ala Pro Arg Asn Asn Gly Arg Tyr Cys
 145 150 155 160
 Thr Gly Lys Arg Ala Ile Tyr Arg Ser Cys Ser Leu Met Pro Cys Pro
 165 170 175
 Pro Asn Gly Lys Ser Phe Arg His Glu Gln Cys Glu Ala Lys Asn Gly
 180 185 190
 Tyr Gln Ser Asp Ala Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro
 195 200 205
 Lys Tyr Ala Ser Val Leu Pro Ser Asp Val Cys Lys Leu Thr Cys Arg
 210 215 220
 Ala Lys Gly Thr Gly Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp
 225 230 235 240
 Gly Thr Glu Cys Arg Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys
 245 250 255
 Cys Val Arg Thr Gly Cys Asp Gly Ile Ile Gly Ser Lys Leu Gln Tyr
 260 265 270
 Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Ile
 275 280 285
 Val Gly Thr Phe Asn Lys Lys Ser Lys Gly Ser Xaa Asp Val Val Arg
 290 295 300
 Ile Pro Glu Gly Ala Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys
 305 310 315 320
 Asp Gln Thr Arg Phe Thr Ala Tyr Leu Ala Leu Lys Lys Lys Asn Gly
 325 330 335
 Glu Tyr Leu Ile Asn Gly Lys Tyr Met Ile Ser Thr Ser Glu Thr Ile
 340 345 350
 Ile Asp Ile Asn Gly Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg
 355 360 365

Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu
 370 375 380
 Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp Val Arg
 385 390 395 400
 Tyr Ser Phe Phe Val Pro Lys Lys Ser Thr Pro Lys Val Asn Ser Val
 405 410 415
 Thr Ser His Gly Ser Asn Lys Val Gly Ser His Thr Ser Gln Pro Gln
 420 425 430
 Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys Asp Thr Gly
 435 440 445
 Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg Lys Leu Ala
 450 455 460
 Lys Gly Cys Pro Leu Ser Gln Arg Pro Ser Ala Phe Lys Gln Cys Leu
 465 470 475 480
 Leu Lys Lys Cys

<210> 17

<211> 423

<212> DNA

<213> Bos taurus

<400> 17

tttagggagg agcagtgtga ggccaaaaat ggatatcagt ctgatgcaaa aggagtcaaa	60
acgtttgtgg aatgggttcc caaatatgct ggtgtcctgc ccggagacgt gtgcaaactg	120
acctgcagag ctaagggcac tggctactac gtggtgttct ctccaaaggt gaccgatggg	180
acagagtgca ggccatacag caattccgtg tgtgtccggg ggaagtgtgt gcggacaggc	240
tgtgacagca tcattggctc gaagctgcag tatgacaaat gtggcgtctg tggaggagac	300
aactccagtt gcacaaaggt ggtcgggaacc ttcaataaaa aaagtaagggt ttacactgac	360
gtcgtgagga tccccgaagg ggcgactcac ataaaagtcc gacagttcaa agccaaagac	420
cag	423

<210> 18

<211> 141

<212> PRT

<213> Bos taurus

<400> 18

Phe Arg Glu Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala	
1 5 10 15	
Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val	
20 25 30	
Leu Pro Gly Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly	
35 40 45	
Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg	
50 55 60	
Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys Cys Val Arg Thr Gly	
65 70 75 80	
Cys Asp Ser Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val	
85 90 95	
Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Val Val Gly Thr Phe Asn	
100 105 110	
Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala	
115 120 125	
Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln	

130

135

140

<210> 19

<211> 637

<212> DNA

<213> Bos taurus

<400> 19

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ggaaaccctg gccatttggg gcaactacct ggccctgaag ctccccgatg gctcctatgc      60
cctcaacggg gaatacacgc tgatcccgtc cccacagac gtggtactgc ccggggccgt      120
cagcctgcgc tacagcgggg cactgcagc ctcgagaca ctgtcaggac acgggcccct      180
ggctgagccc ttaacgctgc aggtcctagt ggctggcaac ccgcagaacg cccgcctcag      240
atacagcttt ttcgtgccgc gaccgcgacc ggtccctcc acgccacgcc cactcccca      300
ggactggctg cgccgcaagt cacagattct ggagatcctc cggcggcgct cctgggccgg      360
caggaaataa cctcaccatc ccggctgccc ttcttgggca ccggggcctc ggacttagct      420
gggtgaacga gagacctctg cagcggcctc accccgagac atcgtggggg aggggcttag      480
tgagccccgc ctctcctccc cgcgtaccg agcaggctgg ccctgccggg gtttcctgcc      540
ctggatggct ggtggatgga aggggctggg agattgtccc ctatctaaac tgccccctct      600
gcctgctgg  tcacaggagg gagggggaag gcaggga                                637

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<210> 20

<211> 122

<212> PRT

<213> Bos taurus

<400> 20

```

Glu Thr Leu Ala Ile Trp Ser Asn Tyr Leu Ala Leu Lys Leu Pro Asp
 1             5             10             15
Gly Ser Tyr Ala Leu Asn Gly Glu Tyr Thr Leu Ile Pro Ser Pro Thr
          20          25          30
Asp Val Val Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr
      35      40      45
Ala Ala Ser Glu Thr Leu Ser Gly His Gly Pro Leu Ala Glu Pro Leu
 50      55      60
Thr Leu Gln Val Leu Val Ala Gly Asn Pro Gln Asn Ala Arg Leu Arg
65      70      75      80
Tyr Ser Phe Phe Val Pro Arg Pro Arg Pro Val Pro Ser Thr Pro Arg
      85      90      95
Pro Thr Pro Gln Asp Trp Leu Arg Arg Lys Ser Gln Ile Leu Glu Ile
      100      105      110
Leu Arg Arg Arg Ser Trp Ala Gly Arg Lys
      115      120

```

<210> 21

<211> 1143

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1143)

<223> n = A,T,C or G

<400> 21

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actcactata gggctcgtgc ggccgcccgg gcaggatatc ttaagcatcc cagcatcctc      60

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aaccccatca acatcgttgt ggtcaaggtg ctgcttctta gagatcgtga ctccggggccc 120
aaggtcaccg gcaatgcggc cctgacgctg cgcaacttct gtgcctggca gaagaagctg 180
aaccaaagtga gtgacaagca ccccgagtac tgggacactg ccacccctct caccaggcag 240
gacctgtgtg gagccaccac ctgtgacacc ctgggcatgg ctgatgtggg taccatgtgt 300
gaccccaaga gaagctgctc tgtcattgag gacgatgggc ttccatcagc cttcaccact 360
gcccacgagc tggggcacgt gttcaacatg ccccatgaca atgtgaaagt ctgtgaggag 420
gtgtttggga agctccgagc caaccacatg atgtccccga ccctcatcca gatcgaccgt 480
gccaaaccct ggtcagcctg cagtgtctgc atcatcaccg actttctgga cagcgggcac 540
ggtgactgcc tcctggacca acccagcaag cccatcttcc tgccgagnga tctgccgggc 600
gccagctaca ccctgagcca gcartgcgag ctggcttttg gcgtgggctt caagccctgt 660
ccttacatgc agtactgcac caagctgtgg tgcaccggga aggccaaggg acagatgggtg 720
tgccaaaccc gccacttccc ctggggcgat ggcaccagtt gtggcgaggg caagttctgc 780
ctcaaagggg cctgcgtgga aaracacaac ctcaacaagc acagggtgga tggttcctgg 840
gccaaatggg atccctatgg cccctgctcg cgcacatgtg gtggggcggt gcagctggcc 900
aggaggcagn tgcaccaacc ccanccttg ccaacngggg gcaagtactg cgagggagtg 960
agggtgaaat accgatcctg caacctggag cctgccccca gctcagcctc cgaaaagagc 1020
ttccgggagg agcagtgtga ggctttcaac ggctacaacc acagcaccaa ccggctcact 1080
ctcgccgtgg catgggtgcc caagtactcc ggcgtgtctc cccgtgacaa gtgtaagctc 1140
atc 1143

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<210> 22

<211> 381

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(381)

<223> Xaa = Any Amino Acid

<400> 22

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Thr His Tyr Arg Ala Arg Ala Ala Arg Ala Gly Ile Phe Lys His
1      5      10      15
Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Lys Val Leu Leu
20     25     30
Leu Arg Asp Arg Asp Ser Gly Pro Lys Val Thr Gly Asn Ala Ala Leu
35     40     45
Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn Lys Val Ser
50     55     60
Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe Thr Arg Gln
65     70     75     80
Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met Ala Asp Val
85     90     95
Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile Glu Asp Asp
100    105    110
Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly His Val Phe
115    120    125
Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val Phe Gly Lys
130    135    140
Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln Ile Asp Arg
145    150    155    160
Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr Asp Phe Leu
165    170    175
Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser Lys Pro Ile
180    185    190

```

Phe Leu Pro Xaa Asp Leu Pro Gly Ala Ser Tyr Thr Leu Ser Gln Gln
 195 200 205
 Cys Glu Leu Ala Phe Gly Val Gly Phe Lys Pro Cys Pro Tyr Met Gln
 210 215 220
 Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly Gln Met Val
 225 230 235 240
 Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser Cys Gly Glu
 245 250 255
 Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Xaa His Asn Leu Asn
 260 265 270
 Lys His Arg Val Asp Gly Ser Trp Ala Lys Trp Asp Pro Tyr Gly Pro
 275 280 285
 Cys Ser Arg Thr Cys Gly Gly Val Gln Leu Ala Arg Arg Gln Xaa
 290 295 300
 His Gln Pro Xaa Pro Leu Pro Thr Gly Gly Lys Tyr Cys Glu Gly Val
 305 310 315 320
 Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro Ser Ser Ala
 325 330 335
 Ser Gly Lys Ser Phe Arg Glu Glu Gln Cys Glu Ala Phe Asn Gly Tyr
 340 345 350
 Asn His Ser Thr Asn Arg Leu Thr Leu Ala Val Ala Trp Val Pro Lys
 355 360 365
 Tyr Ser Gly Val Ser Pro Arg Asp Lys Cys Lys Leu Ile
 370 375 380

<210> 23
 <211> 297
 <212> DNA
 <213> Rattus norvegicus

<400> 23
 tccgcccttc cgggaggaac agtgtgaaaa atataatgcc tacaaccaca cggacctgga 60
 tgggaatttc cttcagtggg tccccaaata ctacaggagtg tccccccgag accgatgcaa 120
 actgttttgc agagcccgtg ggaggagtga gttcaaagtg tttgaaacta aggtgatcga 180
 tggcactctg tgcggaccgg atactctggc catctgtgtg cggggacagt gcgttaaggc 240
 tggctgtgac catgtggtga actcacctaa gaagctggac aagtgcggta tctgtgg 297

<210> 24
 <211> 98
 <212> PRT
 <213> Rattus norvegicus

<400> 24
 Pro Pro Phe Arg Glu Glu Gln Cys Glu Lys Tyr Asn Ala Tyr Asn His
 1 5 10 15
 Thr Asp Leu Asp Gly Asn Phe Leu Gln Trp Val Pro Lys Tyr Ser Gly
 20 25 30
 Val Ser Pro Arg Asp Arg Cys Lys Leu Phe Cys Arg Ala Arg Gly Arg
 35 40 45
 Ser Glu Phe Lys Val Phe Glu Thr Lys Val Ile Asp Gly Thr Leu Cys
 50 55 60
 Gly Pro Asp Thr Leu Ala Ile Cys Val Arg Gly Gln Cys Val Lys Ala
 65 70 75 80
 Gly Cys Asp His Val Val Asn Ser Pro Lys Lys Leu Asp Lys Cys Gly
 85 90 95

Ile Cys

<210> 25
 <211> 823
 <212> DNA
 <213> Rattus norvegicus

<400> 25
 cccttgatg tggtaaagt gcagtcggaa gtacatcacc gagttcttag acactgggta 60
 tggagagtgc ttgttaaagt aacctcaatc caggacctat cctttgcctt cccaactgcc 120
 cggccttctc tacaacgtga ataaacaatg tgaactgatt tttggaccag gctctcaagt 180
 gtgcccatat atgatgcagt gcagacggct ctggtgcaat aacgtggatg gagcacacaa 240
 aggctgcagg actcagcaca cgccctgggc agatggaacc gagtgtgagc ctggaaagca 300
 ctgcaagttt ggattctgtg ttcccaaaga aatggagggc cctgcaattg atggatcctg 360
 gggaggttgg agtcactttg gggcctgctc aagaacatgt ggaggaggca tcagaacagc 420
 catcagagag tgcaacagac cagagccaaa aaatggtggg aggtactgtg tagggaggag 480
 aatraagtcc aaatcctgca acaccgagcc ctgcccgaag cacaagcgag acttccgtga 540
 ggagcagtgt gcttactttg acggcaagca tttcaacatc aatggtctgc tgcccagtgt 600
 acgctgggtc cctaagtaca gtggaatttt gatgaaggac cgatgcaagt tgttctgcag 660
 agtggcagga aacacagcct actaccagct tcgagacaga gtgattgacg gaaccccctg 720
 tggccaggac acaaatgaca tctgtgtcca aggcctttgc cggcaagctg gatgtgatca 780
 tactttaaac tcaaaggccc ggaaagataa atgtgggatt tgt 823

<210> 26
 <211> 274
 <212> PRT
 <213> Rattus norvegicus

<220>
 <221> VARIANT
 <222> (1)...(274)
 <223> Xaa = Any Amino Acid

<400> 26
 Pro Trp Met Trp Ser Lys Cys Ser Arg Lys Tyr Ile Thr Glu Phe Leu
 1 5 10 15
 Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Gln Ser Arg Thr
 20 25 30
 Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu Leu Tyr Asn Val Asn Lys
 35 40 45
 Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro Tyr Met
 50 55 60
 Met Gln Cys Arg Arg Leu Trp Cys Asn Asn Val Asp Gly Ala His Lys
 65 70 75 80
 Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr Glu Cys Glu
 85 90 95
 Pro Gly Lys His Cys Lys Phe Gly Phe Cys Val Pro Lys Glu Met Glu
 100 105 110
 Gly Pro Ala Ile Asp Gly Ser Trp Gly Ser Trp Ser His Phe Gly Ala
 115 120 125
 Cys Ser Arg Thr Cys Gly Gly Gly Ile Arg Thr Ala Ile Arg Glu Cys
 130 135 140
 Asn Arg Pro Glu Pro Lys Asn Gly Gly Arg Tyr Cys Val Gly Arg Arg
 145 150 155 160

Xaa Lys Phe Lys Ser Cys Asn Thr Glu Pro Cys Pro Lys His Lys Arg
 165 170 175
 Asp Phe Arg Glu Gln Cys Ala Tyr Phe Asp Gly Lys His Phe Asn
 180 185 190
 Ile Asn Gly Leu Leu Pro Ser Val Arg Trp Val Pro Lys Tyr Ser Gly
 195 200 205
 Ile Leu Met Lys Asp Arg Cys Lys Leu Phe Cys Arg Val Ala Gly Asn
 210 215 220
 Thr Ala Tyr Tyr Gln Leu Arg Asp Arg Val Ile Asp Gly Thr Pro Cys
 225 230 235 240
 Gly Gln Asp Thr Asn Asp Ile Cys Val Gln Gly Leu Cys Arg Gln Ala
 245 250 255
 Gly Cys Asp His Thr Leu Asn Ser Lys Ala Arg Lys Asp Lys Cys Gly
 260 265 270
 Ile Cys

<210> 27

<211> 1073

<212> PRT

<213> Homo sapien

<400> 27

Met Gln Phe Val Ser Trp Ala Thr Leu Leu Thr Leu Leu Val Arg Asp
 1 5 10 15
 Leu Ala Glu Met Gly Ser Pro Asp Ala Ala Ala Val Arg Lys Asp
 20 25 30
 Arg Leu His Pro Arg Gln Val Lys Leu Leu Glu Thr Leu Gly Glu Tyr
 35 40 45
 Glu Ile Val Ser Pro Ile Arg Val Asn Ala Leu Gly Glu Pro Phe Pro
 50 55 60
 Thr Asn Val His Phe Lys Arg Thr Arg Arg Ser Ile Asn Ser Ala Thr
 65 70 75 80
 Asp Pro Trp Pro Ala Phe Ala Ser Ser Ser Ser Ser Thr Ser Ser
 85 90 95
 Gln Ala His Tyr Arg Leu Ser Ala Phe Gly Gln Gln Phe Leu Phe Asn
 100 105 110
 Leu Thr Ala Asn Ala Gly Phe Ile Ala Pro Leu Phe Thr Val Thr Leu
 115 120 125
 Leu Gly Thr Pro Gly Val Asn Gln Thr Lys Phe Tyr Ser Glu Glu Glu
 130 135 140
 Ala Glu Leu Lys His Cys Phe Tyr Lys Gly Tyr Val Asn Thr Asn Ser
 145 150 155 160
 Glu His Thr Ala Val Ile Ser Leu Cys Ser Gly Met Leu Gly Thr Phe
 165 170 175
 Arg Ser His Asp Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp
 180 185 190
 Glu Gln Glu Asp Glu Glu Glu Gln Asn Lys Pro His Ile Tyr Arg
 195 200 205
 Arg Ser Ala Pro Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp
 210 215 220
 Thr Ser Glu His Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg
 225 230 235 240
 Ala Arg Lys Trp Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala
 245 250 255
 Leu Asn Ser Gly Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys

260	265	270
Thr Asp Asn Thr Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe		
275	280	285
Leu Ser Tyr Pro Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg		
290	295	300
Met Val Ser Tyr His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu		
305	310	315
Met Ser Ile Val Ala Ser Ile Tyr Lys Asp Pro Ser Ile Gly Asn Leu		
325	330	335
Ile Asn Ile Val Ile Val Asn Leu Ile Val Ile His Asn Glu Gln Asp		
340	345	350
Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Leu Cys		
355	360	365
Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr		
370	375	380
Ala Val Leu Leu Thr Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys		
385	390	395
Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg		
405	410	415
Ser Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile		
420	425	430
Ala His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn		
435	440	445
Lys Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro		
450	455	460
Thr Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg		
465	470	475
Lys Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu		
485	490	495
Asn Glu Pro Glu Ser Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly		
500	505	510
Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly		
515	520	525
Ser Gln Val Cys Pro Tyr Met Gln Cys Arg Arg Leu Trp Cys Asn		
530	535	540
Asn Val Asn Gly Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp		
545	550	555
Ala Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Tyr Gly Phe		
565	570	575
Cys Val Pro Lys Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly		
580	585	590
Ser Trp Ser Pro Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile		
595	600	605
Lys Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly		
610	615	620
Lys Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu		
625	630	635
Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His		
645	650	655
Phe Asp Gly Lys His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg		
660	665	670
Trp Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu		
675	680	685
Phe Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg		
690	695	700

Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 705 710 715 720
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 725 730 735
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 740 745 750
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr
 755 760 765
 Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
 770 775 780
 Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
 785 790 795 800
 Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
 805 810 815
 Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
 820 825 830
 Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
 835 840 845
 Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
 850 855 860
 Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
 865 870 875 880
 Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
 885 890 895
 Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
 900 905 910
 Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
 915 920 925
 Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
 930 935 940
 Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
 945 950 955 960
 Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
 965 970 975
 Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
 980 985 990
 Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
 995 1000 1005
 Cys Lys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile
 1010 1015 1020
 Cys Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His
 1025 1030 1035 1040
 Gln Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln
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 1060 1065 1070
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<210> 28

<211> 951

<212> PRT

<213> Mus musculus

<400> 28

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Arg Gly Ala His Gly Arg Pro Thr Glu Glu Asp Glu Glu Leu Val Leu			
35	40	45	
Pro Ser Leu Glu Arg Ala Pro Gly His Asp Ser Thr Thr Thr Arg Leu			
50	55	60	
Arg Leu Asp Ala Phe Gly Gln Gln Leu His Leu Lys Leu Gln Pro Asp			
65	70	75	80
Ser Gly Phe Leu Ala Pro Gly Phe Thr Leu Gln Thr Val Gly Arg Ser			
85	90	95	
Pro Gly Ser Glu Ala Gln His Leu Asp Pro Thr Gly Asp Leu Ala His			
100	105	110	
Cys Phe Tyr Ser Gly Thr Val Asn Gly Asp Pro Gly Ser Ala Ala Ala			
115	120	125	
Leu Ser Leu Cys Glu Gly Val Arg Gly Ala Phe Tyr Leu Gln Gly Glu			
130	135	140	
Glu Phe Phe Ile Gln Pro Ala Pro Gly Val Ala Thr Glu Arg Leu Ala			
145	150	155	160
Pro Ala Val Pro Glu Glu Glu Ser Ser Ala Arg Pro Gln Phe His Ile			
165	170	175	
Leu Arg Arg Arg Arg Gly Ser Gly Gly Ala Lys Cys Gly Val Met			
180	185	190	
Asp Asp Glu Thr Leu Pro Thr Ser Asp Ser Arg Pro Glu Ser Gln Asn			
195	200	205	
Thr Arg Asn Gln Trp Pro Val Arg Asp Pro Thr Pro Gln Asp Ala Gly			
210	215	220	
Lys Pro Ser Gly Pro Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser			
225	230	235	240
Pro Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Asp			
245	250	255	
Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val			
260	265	270	
Ala Ala Arg Phe Tyr Lys His Pro Ser Ile Arg Asn Ser Ile Ser Leu			
275	280	285	
Val Val Val Lys Ile Leu Val Ile Tyr Glu Glu Gln Lys Gly Pro Glu			
290	295	300	
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln			
305	310	315	320
Lys Gln His Asn Ser Pro Ser Asp Arg Asp Pro Glu His Tyr Asp Thr			
325	330	335	
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser His Thr Cys Asp			
340	345	350	
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser			
355	360	365	
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala			
370	375	380	
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys His			
385	390	395	400
Cys Ala Ser Leu Asn Gly Val Thr Gly Asp Ser His Leu Met Ala Ser			
405	410	415	
Met Leu Ser Ser Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala			
420	425	430	
Tyr Met Val Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met			
435	440	445	

Asp Lys Pro Gln Asn Pro Ile Lys Leu Pro Ser Asp Leu Pro Gly Thr
 450 455 460
 Leu Tyr Asp Ala Asn Arg Gln Cys Gln Phe Thr Phe Gly Glu Glu Ser
 465 470 475 480
 Lys His Cys Pro Asp Ala Ala Ser Thr Cys Thr Thr Leu Trp Cys Thr
 485 490 495
 Gly Thr Ser Gly Gly Leu Leu Val Cys Gln Thr Lys His Phe Pro Trp
 500 505 510
 Ala Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Val Ser Gly Lys
 515 520 525
 Cys Val Asn Lys Thr Asp Met Lys His Phe Ala Thr Pro Val His Gly
 530 535 540
 Ser Trp Gly Pro Trp Gly Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly
 545 550 555 560
 Gly Gly Val Gln Tyr Thr Met Arg Glu Cys Asp Asn Pro Val Pro Lys
 565 570 575
 Asn Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys
 580 585 590
 Asn Ile Glu Asp Cys Pro Asp Asn Gly Lys Thr Phe Arg Glu Glu
 595 600 605
 Gln Cys Glu Ala His Asn Glu Phe Ser Lys Ala Ser Phe Gly Asn Glu
 610 615 620
 Pro Thr Val Glu Trp Thr Pro Lys Tyr Ala Gly Val Ser Pro Lys Asp
 625 630 635 640
 Arg Cys Lys Leu Thr Cys Glu Ala Lys Gly Ile Gly Tyr Phe Phe Val
 645 650 655
 Leu Gln Pro Lys Val Val Asp Gly Thr Pro Cys Ser Pro Asp Ser Thr
 660 665 670
 Ser Val Cys Val Gln Gly Gln Cys Val Lys Ala Gly Cys Asp Arg Ile
 675 680 685
 Ile Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val Cys Gly Gly Asn
 690 695 700
 Gly Ser Thr Cys Lys Lys Met Ser Gly Ile Val Thr Ser Thr Arg Pro
 705 710 715 720
 Gly Tyr His Asp Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Glu
 725 730 735
 Val Lys His Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu
 740 745 750
 Ala Ile Arg Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asn Phe Thr
 755 760 765
 Leu Ser Thr Leu Glu Gln Asp Leu Thr Tyr Lys Gly Thr Val Leu Arg
 770 775 780
 Tyr Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro
 785 790 795 800
 Leu Lys Glu Pro Leu Thr Ile Gln Val Leu Met Val Gly His Ala Leu
 805 810 815
 Arg Pro Lys Ile Lys Phe Thr Tyr Phe Met Lys Lys Lys Thr Glu Ser
 820 825 830
 Phe Asn Ala Ile Pro Thr Phe Ser Glu Trp Val Ile Glu Glu Trp Gly
 835 840 845
 Glu Cys Ser Lys Thr Cys Gly Ser Gly Trp Gln Arg Arg Val Val Gln
 850 855 860
 Cys Arg Asp Ile Asn Gly His Pro Ala Ser Glu Cys Ala Lys Glu Val
 865 870 875 880
 Lys Pro Ala Ser Thr Arg Pro Cys Ala Asp Leu Pro Cys Pro His Trp

<210> 32
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Semiconserved sequence of ADAMTS protein domain
that binds to the extracellular matrix

<400> 32
Phe Arg Glu Glu Gln Cys
1 5

<210> 33
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide derived from analysis of the
sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
<222> (1)...(18)
<223> n = A,T,C or G

<400> 33
ttymgngarg arcartgy

18

<210> 34
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide derived from analysis of the
sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
<222> (1)...(18)
<223> n = A,T,C or G

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rcanaynccr cayttrtc

18

<210> 35
<211> 4
<212> PRT
<213> Homos sapien

<220>
<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT
<222> (3) ... (3)
<223> Xaa = Lysine or Arginine

<221> VARIANT
<222> (1) ... (4)
<223> Xaa = Any Amino Acid

<400> 35
Arg Xaa Xaa Arg
1

<210> 36
<211> 7
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<221> VARIANT
<222> (2) ... (2)
<223> Xaa = Serine or Glycine

<221> VARIANT
<222> (1) ... (7)
<223> Xaa = Any Amino Acid

<400> 36
Trp Xaa Xaa Trp Ser Xaa Trp
1 5

<210> 37
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<400> 37
Cys Ser Val Thr Cys Gly
1 5

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 38

caggggaaac agacgatgac aact

24

<210> 39

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<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 39

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21

<210> 40

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 40

gtgcgctggg tccctaaata c

21

<210> 41

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 41

aaaatcacag gttggcagcg g

21

<210> 42

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 42

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1

5

10

<210> 43

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 43

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<210> 44

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 44

His Glu Ile Gly His Asn Phe Gly Ser Pro His Asp
1 5 10

<210> 45

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<213> Homo sapien

<400> 45

His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

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<212> PRT

<213> Homo sapien

<400> 46

His Glu Thr Gly His Val Leu Gly Met Glu His Asp
1 5 10

<210> 47

<211> 12

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His Glu Leu Gly His Val Phe Asn Met Leu His Asp
1 5 10

<210> 48

<211> 12

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<213> Homo sapien

<400> 48

His Glu Ile Gly His Leu Leu Gly Leu Ser His Asp
1 5 10

<210> 49

<211> 12

<212> PRT

<213> Homo sapien

<400> 49

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1 5 10

<210> 50

<211> 12

<212> PRT

<213> C. elegans

<400> 50

His Glu Leu Gly His Val Phe Ser Ile Pro His Asp
1 5 10

<210> 51

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT

<222> (1)...(12)

<223> Xaa = Any Amino Acid

<400> 51

His Glu Xaa Gly His Xaa Xaa Gly Xaa Xaa His Asp
1 5 10

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(74) Agents: CHRISTIANSEN, William, T. et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).

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(71) Applicant (for all designated States except US): NEUROCRINE BIOSCIENCES, INC. [US/US]; 10555 Science Center Drive, San Diego, CA 92121 (US).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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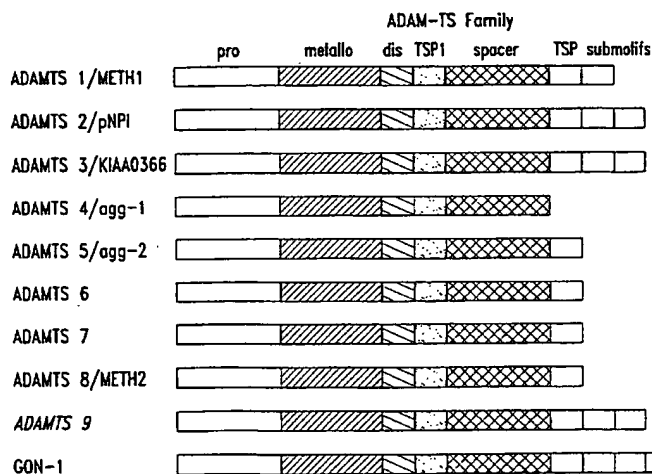
Published:

— With international search report.

(88) Date of publication of the international search report:
18 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR



(57) Abstract: Members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.

WO 00/53774 A3

INTERNATIONAL SEARCH REPORT

International Application No

/US 00/06237

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/57 C12N15/63 C12N9/64 A61K38/48 C07K16/40
C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 98 55643 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 10 December 1998 (1998-12-10)</p> <p>& EP 1 004 674 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 31 May 2000 (2000-05-31)</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1,3-11, 17-21, 28,29, 31,32</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

29 June 2000

Date of mailing of the international search report

13.10.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

MONTERO LOPEZ B.

INTERNATIONAL SEARCH REPORT

International Application No

P./US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KOUJI KUNO ET AL.: "Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 1, 3 January 1997 (1997-01-03), pages 556-562, XP002076038 MD US cited in the application abstract page 558, left-hand column, paragraph 2 -page 559, left-hand column, paragraph 2; figure 2 page 559, left-hand column, paragraph 4 page 561, right-hand column, last paragraph -page 562, left-hand column, paragraph 1</p>	1,3-11, 17,20, 21,28, 29,31,32
X	<p>--- KOUJI KUNO ET AL.: "The exon/intron organization and chromosomal mapping of the mouse ADAMTS-1 gene encoding an ADAM family protein with TPS motifs" GENOMICS, vol. 46, no. 3, 15 December 1997 (1997-12-15), pages 466-471, XP000922766 cited in the application page 466, right-hand column, paragraph 2 page 468, left-hand column, paragraph 5 -page 470, right-hand column, paragraph 2; figure 3</p>	1,3-11
X	<p>--- BOR LUEN TANG ET AL.: "ADAMTS: A novel family of proteases with an ADAM protease domain and thrombospondin 1 repeats" FEBS LETTERS, [Online] vol. 445, 26 February 1999 (1999-02-26), pages 223-225, XP002141413 AMSTERDAM NL Retrieved from the Internet: <URL:http://gdbwww.gdb.org/gdb-bin/genera/ genera/hgd/Gene?!action=query&displayName= ADAMTS2> [retrieved on 2000-06-22] page 223, left-hand column, paragraph 2 -page 225, right-hand column, paragraph 2; figure 2</p>	1,3-11
X	<p>--- EMBL Database Entry A1378857 Accession number A1378857; 28 January 1999 ROBERT STRAUSBERG:"tc67h11.x1 Soares_NhHMPu_S1 Homo sapiens cDNA clone" XP002141415 the whole document ---</p>	1,5-7

INTERNATIONAL SEARCH REPORT

International Application No

P /US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>FRANCISCA VÁZQUEZ ET AL.: "METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 33, 13 August 1999 (1999-08-13), pages 23349-23357, XP002141414 MD US abstract page 23349, right-hand column, paragraph 2 -page 23350, left-hand column, paragraph 1 page 23351, left-hand column, paragraph 1 -page 23352, right-hand column, paragraph 2; figure 1 page 23353, left-hand column, paragraph 4 -page 23357, left-hand column, paragraph 2 -----</p>	1,3-6, 8-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/06237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 22-27, 30, 33-35
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-12, 17-35 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 22-27, 30, 33-35

Present claims 22-27, 30 and 33-35 relate to an agent defined by reference to a desirable characteristic or property, namely decreasing or modulating expression or activity of an ADAMTS protein. The claims cover all agents having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any specific example of such agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agent by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 22-27, 30 and 33-35.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:1 or 23 encoding ADAMTS-2; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-2 polypeptide; ADAMTS-2 polypeptide of SEQ ID NO:2 or 24 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-2 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-2 protein

2. Claims: 36 and partially 1-12, 17-35

Polynucleotide of SEQ ID NO:3, 15 or 17 encoding ADAMTS-4; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-4 polypeptide; ADAMTS-4 polypeptide of SEQ ID NO:4, 16 or 18 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-4 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-4 protein

3. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:9 or 25 encoding ADAMTS-3; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-3 polypeptide; ADAMTS-3 polypeptide of SEQ ID NO:10 or 26 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-3 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-3 protein

4. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:13 or 21 encoding ADAMTS-5; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-5 polypeptide; ADAMTS-5 polypeptide of SEQ ID NO:13 or 21 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-5 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-5 protein

5. Claims: Partially, 1, 3-12, 17-35

Polynucleotide encoding an ADAMTS-9 protein of SEQ ID NO:27;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-9 polypeptide; ADAMTS-9 polypeptide of SEQ ID NO:27 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-9 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-9 protein

6. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:6 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:6 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

7. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:8 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:8 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

8. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:12 or 20 or variants thereof; ADAMTS polypeptide of SEQ ID NO:12 or 20 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

Information on patent family members

F ./US 00/06237

Patent document
cited in search report

Publication date

Patent family member(s)

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